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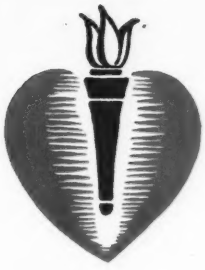

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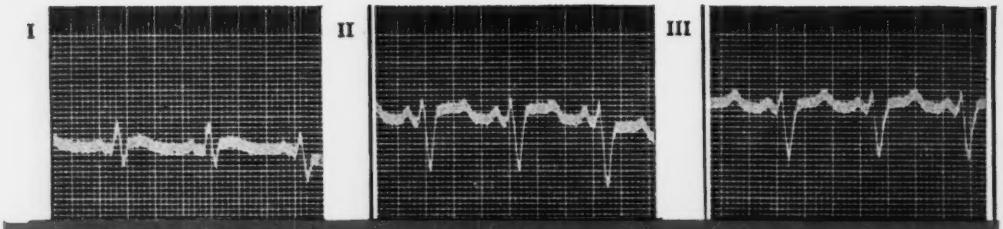

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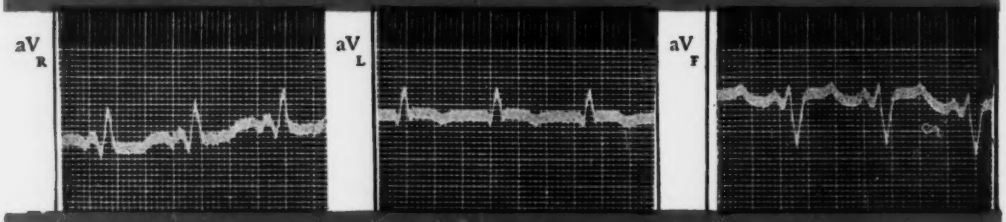

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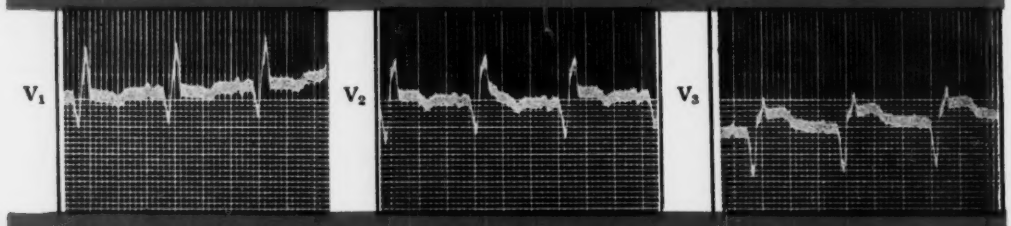

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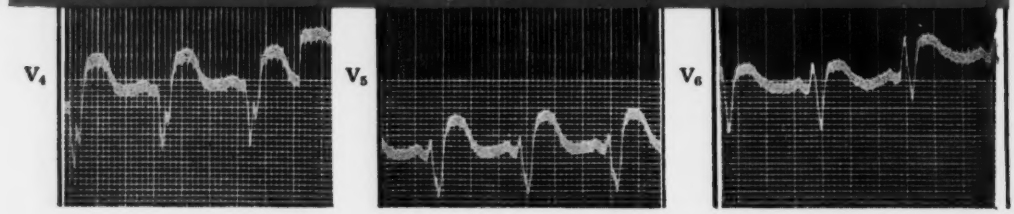

Circulation

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Evidence for Increased Serum Glutamic Oxalacetic Transaminase (SGO-T) Activity Following Graded Myocardial Infarcts in Dogs

By IRWIN NYDICK, M.D., FELIX WRÓBLEWSKI, M.D. AND JOHN S. LADUE, M.D., PH.D.

Elevation in serum concentration of the enzyme, glutamic oxalacetic transaminase, (SGO-T), is an accurate index of myocardial infarction in dogs. The enzyme rises in a rough proportion to the extent of myocardial necrosis. The test is a sensitive guide to myocardial injury. Infarcts less than 1 Gm. in weight result in a significant alteration in serum concentration of the enzyme. Concentrations of the enzyme in infarcted muscle are markedly lower than in normal muscle, suggesting that seepage through damaged cells causes the rise in serum concentration. Experimental and clinical myocardial injury result in similar abnormalities.

GLUTAMIC oxalacetic transaminase (GO-T) has been found to be present in all human sera that have been tested. Comparable concentrations are found whether the more laborious chromatographic method is used or whether the relatively simple and rapid spectrophotometric assay is employed.[1] When serum is added to excesses of aspartic acid and alpha ketoglutaric acid buffered at optimal pH in the presence of coenzyme 1 ($DPNH^+$) and malic dehydrogenase, serum glutamic oxalacetic transaminase can be measured in a spectrophotometer by the decrease in optical density resulting from the oxidation of reduced diphosphopyridine nucleotide ($DPNH^+$) to the oxidized form of the enzyme (DPN). (See fig. 1.) Other workers have been measuring the concentration of glutamic oxalacetic transaminase (GO-T) in various animal tissues and have found the enzyme in high concentration in heart muscle, skeletal muscle, brain, liver, and kidney in decreasing order.[2, 3] This property led us to study serum levels following acute myocardial infarction in human subjects. Serum glutamic oxalacetic transaminase (SGO-T) rises 2 to 20 times above the upper limits of normal within 6 to 72 hours after infarction.[4]

Dogs subjected to experimental myocardial infarction by injection of plastic microspheres into the coronary circulation invariably exhibit a rise in serum transaminase 6 to 48 hours after injury, which is apparently roughly proportional to the amount of myocardial necrosis.[5] The enzyme has also been found elevated when myocardial necrosis was produced in rabbits by the intravenous injection of papain.[6, 11] The first of these methods subjects the dogs to prolonged anesthesia and possibly secondary liver damage. In the second, the possibility of the effect of papain upon other transaminase-rich tissues cannot be excluded. Striking elevations in serum glutamic oxalacetic transaminase follow acute liver damage, and lesser rises occur after acute renal or skeletal muscle damage.[7, 8] In order to exclude serum transaminase elevation due to injury to hepatic, renal or other transaminase sources, we used the method de-

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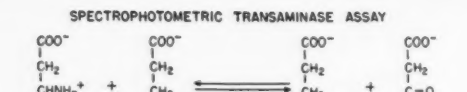

FIG. 1. Shows the chemical reactions involved in measuring the serum glutamic oxalacetic transaminase.

veloped by LeRoy and associates for inducing acute myocardial necrosis experimentally.[9]

The purpose of these studies was to answer the following questions, if possible. 1. Does the serum concentration of glutamic oxalacetic transaminase invariably rise following myocardial necrosis? 2. What is the smallest infarction that would elevate the serum level of transaminase? 3. Will the serum glutamic oxalacetic transaminase rise without infarction but after ischemia? 4. Will the operative procedure employed affect the level in the serum? 5. Is glutamic oxalacetic transaminase released from necrotic muscle or is it produced elsewhere as a nonspecific response? 6. What is the mechanism of serum glutamic oxalacetic transaminase elevation following experimental myocardial infarction?

METHODS

Measurement of Enzyme

The serum levels of glutamic oxalacetic transaminase were analyzed by a spectrophotometric method.[1] The reaction is based on a double enzyme system with all substrates present in excess; the limiting factor is the concentration of glutamic oxalacetic transaminase in the serum.

The only actual measurement in the assay of the rate of this reaction is the spectrophotometric analysis of the decrease in optical density as oxidized diphosphopyridine nucleotide (DPN, coenzyme 1) is formed from the reduced enzyme ($DPNH^+$). The rate is dependent on the concentration of serum transaminase. One unit is designated as a change in optical density of .001 per milliliter per minute at wave length 340 mμ. The normal range is 8 to 40 units per milliliter per minute (fig. 1).

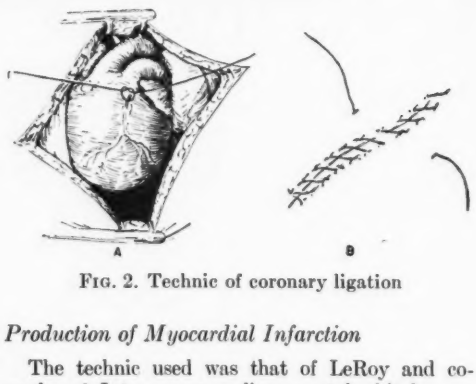

FIG. 2. Technic of coronary ligation

Production of Myocardial Infarction

The technic used was that of LeRoy and coworkers.[9] Intravenous sodium pentobarbital anesthesia was administered and respiration sustained by intermittent positive pressure oxygen through tracheal intubation. No dog was anesthetized for more than three hours. A left lateral chest incision was made, the fourth rib resected, and nooses of braided silk loosely placed around chosen branches of coronary arteries. The ends of the tie were brought out through stab wounds in the chest at right angles to the artery and buried subcutaneously (fig. 2). The advantage of this method is that the myocardial infarct can be produced at any chosen interval subsequent to the operation at a time when the serum glutamic oxalacetic transaminase has returned to normal limits. In this way we separate the alteration of serum concentration of transaminase which results from surgery from that due to coronary ligation.

Before infarction, the dogs were given morphine sulphate subcutaneously (up to 30 mg. are usually necessary to abolish pain), 0.1 mg. atropine sulphate intravenously per kilogram of body weight and 15 mg. of aminophylline intravenously per kilogram of body weight. The appropriate ties were then drawn tight, occluding the coronary artery, and serial venous bloods and electrocardiograms were obtained.* The observations of LeRoy and associates[9] on the diminution of mortality following this premedication were substantially confirmed in our experiments.

Homogenates

Homogenates of infarcted and normal areas of dog heart were prepared in an ice-water bath as soon after death of the animal as possible. When tissues were not homogenized at once, they were quick frozen and stored in dry ice. Homogenization of saline suspensions of minced muscle was complete

* All electrocardiograms were recorded with the Poly-Viso (Sanborn), a direct writing machine, usually at a paper speed of 50 mm. per minute.

except for very small amounts of residual collagen. Calculations of transaminase content were based on the wet weight of the fresh heart muscle.

The spectrophotometric analysis was performed in the standard fashion. At least 10 minutes were allowed for the blank reaction before the addition of alpha ketoglutarate, in the same manner as previously described for the assay of serum. A dilution of the homogenate of 1:1000 to 1:1500 was utilized in the analyses. It was noted that the "blank" reaction ceased or slowed to a very low rate within the allotted interval when using this dilution. The addition of the alpha ketoglutarate always resulted in the expected rapid decrement of optical density as the transamination reaction then proceeded.

Results

Sixteen dogs had 18 operations with an immediate operative mortality of three and a postoperative mortality of two (total 28 per cent). In the 11 remaining dogs 10 infarcts were produced in nine dogs with a mortality of 10 per cent. One dog failed to develop infarction after coronary ligation. One animal (control) had a thoracotomy without disturbing the heart or opening the pericardium.

In the one dog with thoracotomy alone, the serum glutamic oxalacetic transaminase rose to 60 units within 12 hours and fell to normal in four days. In another a second rise up to 40 units occurred on the seventh and eighth days, thereafter falling and remaining below 40 units. The first rise we attribute to skeletal muscle damage at operation with consequent release of transaminase and the second, possibly to liver dysfunction as a result of anesthesia and other causes. These early transaminase elevations were noted following every operation done in this study whether or not the pericardium was entered.

Figure 3 shows the postoperative elevation until the fourth day. On the fifth day the ligature previously placed about the left coronary artery was pulled tight. Five hours later the serum glutamic oxalacetic transaminase was 86 units; at seven hours post ligation the level was 120 units and within 17 hours had risen to 274 units, returning to normal 72 hours after ligation. At autopsy fresh infarction of the anterior wall and anterior portion of the interventricular septum was found. (See fig. 4.)

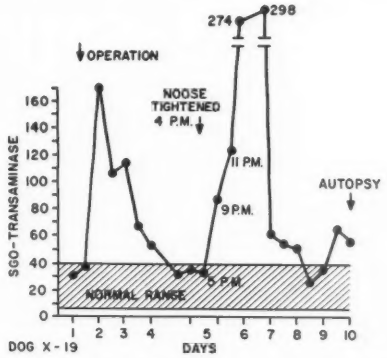

FIG. 3. Shows the level of transaminase following placement of a ligature about the left coronary artery and after ligation of this vessel with the resulting myocardial infarction shown in figure 4.

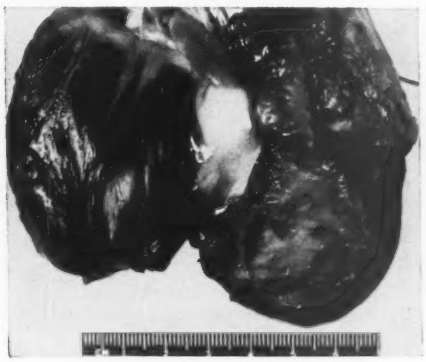

FIG. 4. Infarct produced by procedure described in legend of figure 3.

Figure 5 shows the serum levels of glutamic oxalacetic transaminase following a minute apical infarction. On the first day of the experiment, a "blank" operation (interruption of the pectorals and removal of a rib) was performed. The level rose following operation. On the fourteenth day, the chest was re-entered and ties were loosely placed around a terminal branch of the left anterior descending coronary artery. The level again rose following operation. On the twenty-first day after the original operation, the ligature was pulled tight and an apical myocardial infarct produced. The serum transaminase rose to 120 units, falling to normal limits within 24 hours. The cause of the

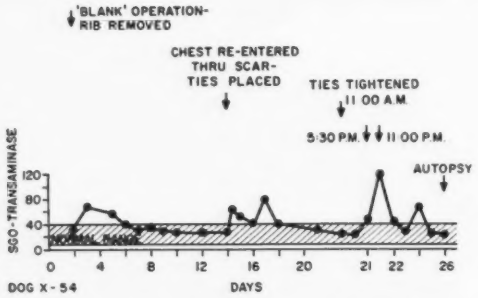

FIG. 5. Shows variation in serum glutamic oxalacetic transaminase following a blank operation, then following the placing of ties about a terminal branch of a coronary artery and then after ligature, with the resulting infarct shown in figure 6.

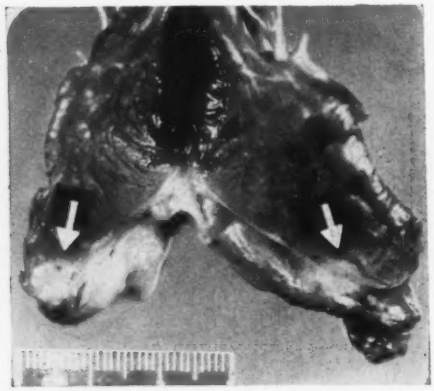

FIG. 6. Infarct produced by procedure described in legend of figure 5.

second elevation 48 hours later to 75 units prior to autopsy is not clear. The heart of this dog contained a fresh apical infarct weighing less than 1 Gm. (See fig. 6.)

Table 1 shows the relationship between the size of the myocardial infarct and the peak level of the serum glutamic oxalacetic transaminase as well as the *duration* of the rise. In general, the larger the size of the myocardial infarct, the higher the maximum rise of serum transaminase and the longer the duration of elevation. That we did not see an absolutely linear relationship between the size of the infarction, as seen at autopsy, and the peak or duration of transaminase abnormality is not surprising, considering the many variables that might influence this curve, i.e., variations in blood volume (size of "diluting medium") in

TABLE 1.—*Relationship of Size of Infarct to Height and Duration of Serum Glutamic Oxalacetic Transaminase (SGO-T) Elevation.*

Dog	Weight Infarct	SGO-T Maximum	Duration SGO-T Elevation
X-110	16 Gm. plus	491	4 days
X-2	18 Gm.	423	2.5 days
X-79* (Large artery)	18 Gm.*	312	2.5 days
X-19	15 Gm.	288	3 days
X-33	4 Gm.	130†	20 hours†
X-54	Less than 1 Gm.	120	1 day (and brief rebound)
X-79* (Small artery)	18 Gm.*	116	1 day
X-17	Less than 1 Gm.	85	5 days
X-52	0.5 Gm.	64	1 day
X-14	Died 2 hours after infarction		

* Two separate infarcts—not demarcated grossly at autopsy.

† Sacrificed 20 hours after infarction.

Note: The size of the infarct, the maximum level of serum glutamic oxalacetic transaminase seen after infarction and the duration of the SGO-T elevation. Two infarcts were produced in dog X-79, one week apart. They could not be demarcated at autopsy.

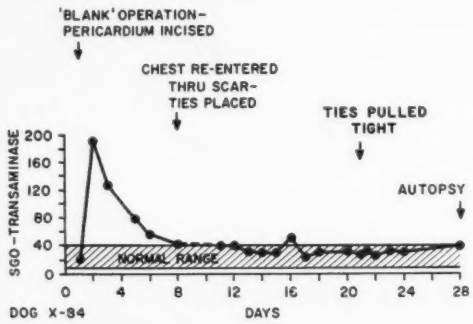

FIG. 7. Depicts transaminase levels following thoracotomy with the failure to rise following ligation of the main left circumflex coronary artery on day 20. See text for discussion.

different sized animals, rapidity of necrosis, completeness of necrosis, rate of removal and breakdown of the enzyme, original concentrations of enzyme in the individual normal heart muscle, and other factors. It was unexpected that as close a relationship existed as reported.

Figure 7 describes an unusual experiment.

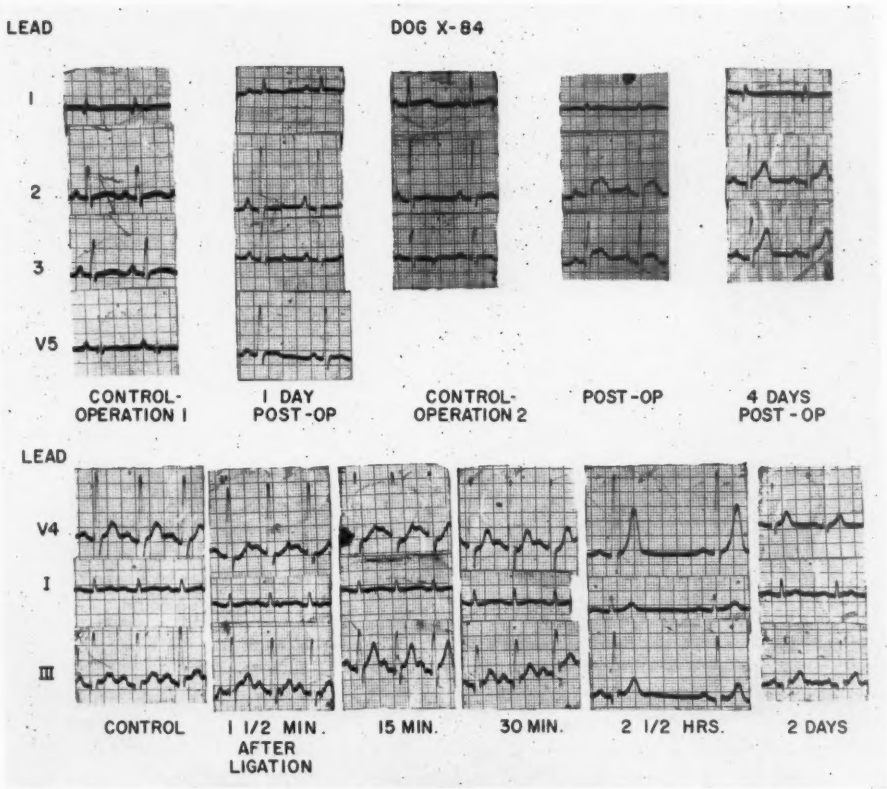

FIG. 8. Shows the electrocardiographic changes seen in the dog whose transaminase levels are described in figure 7.

On day zero a thoracotomy was done and the pericardium opened. This was followed by elevation of the serum glutamic oxalacetic transaminase to 180 units which fell to normal on the eighth day. Then the chest was re-entered through scar tissue and the ligature placed about a main branch of the left coronary artery. No blood samples were obtained for three days following this operation. On day 21 the tie was tightened and the artery completely occluded. The level remained below 40 units for the eight days until the animal was sacrificed. At autopsy, although the ligature was completely occluding the main left circumflex artery, no gross or microscopic evidence of infarction was present.

The electrocardiograms in the upper row (fig. 8) show the ST-T wave changes of pericarditis following the two operations on the heart. The tracing returned to normal before the main left circumflex artery was occluded. The electrocardiograms in the lower row show progressive S-T elevation in lead III with reciprocal depression in V_4 and T-wave changes. The tracing returned toward normal at 30 minutes and became completely normal within 45 minutes. The different form of the T wave at two and one-half hours may be attributed to the change in heart rate. No Q wave is seen.

In this experiment it was planned to produce a large posterior myocardial infarction. However, despite the fact that the animal was prepared in the routine fashion and the tie was proved at autopsy to have completely occluded the main trunk of the left circumflex coronary artery, only S-T and T-wave changes were seen on the electrocardiogram which spontaneously

TABLE 2.—*Transaminase Concentrations in Normal and Infarcted Heart Muscle (Units/Gm.)*

Dog	Normal Muscle	Infarcted Muscle	Age of Infarct	Ratio Concentration Normal to Infarcted Myocardium
X-49	200,000	—	—	—
X-14	305,400	230,400	2 hours	1.3/1
X-33	451,000	218,600	20 hours	2/1
X-110	465,000	23,000	7 days	11/1
X-79	348,000	33,200	7 days	20/1
X-2	250,000	5,600	9 days	45/1

This table compares the glutamic oxalacetic transaminase content of normal heart muscle with that of necrotic heart muscle of dogs (each dog being his own control) at varying times after infarction. Dog X-14 showed evidence of very early infarction on microscopic examination only, having died two hours following coronary ligation.

reverted to normal within 45 minutes. No Q-wave changes of necrosis were seen and the serum glutamic oxalacetic transaminase did not rise following ligation of the coronary artery. At autopsy the myocardium was perfectly normal despite the fact that the main left circumflex artery was completely occluded. This presented a fortuitous situation in which spontaneously reversible electrocardiographic changes of ischemia and injury were seen.[10] No necrosis was found in the myocardium at autopsy.

The reasons why no myocardial infarction was produced are not apparent, unless the atropine-aminophylline premedication completely protected the area of myocardium supplied by this artery. We believe that this combination of findings indicates that a rise in the serum glutamic oxalacetic transaminase may result from leakage of enzyme through severely damaged cell membranes and does not occur after ischemia of short duration.

Transaminase Concentration in Normal and Infarcted Heart Muscle

Further support for the concept that transaminase is released into the blood stream only from a necrotic area of heart muscle is provided by the observations on the concentration of this enzyme in normal and infarcted muscle.

If serum enzyme levels remain normal following reversible functional abnormalities in the heart, one might expect that in situations of irreversible damage (i.e., necrosis) a rise in serum enzyme concentration is the result of loss of this enzyme into the blood stream from the necrotic area. Indirect evidence for this is presented in table 2. It can be seen that there is a much smaller concentration of enzyme in the necrotic heart muscle than in normal heart muscle from the same animal. In addition, it would appear that the older infarcts have released more transaminase than the recent ones, and thus the loss of enzyme is a function of the duration as well as the amount of necrosis. The ratio of enzyme in normal to infarcted muscle as high as 45:1 (dog X-2) is especially striking.

DISCUSSION

The serum glutamic oxalacetic transaminase was invariably elevated following myocardial infarction in the dogs studied. The height of the rise of the enzyme in the sera as well as the duration of the rise was roughly proportional to the amount of infarcted heart muscle. These findings were strikingly similar to those reported following transmural myocardial infarction in man. In the latter the height and duration of transaminase activity also appeared to be correlated with the size of the infarct. The sensitivity of the test is attested to by the fact that infarcts less than 1 Gm. in size resulted in significant, but short, elevations of the serum transaminase (dog X-54, X-52 and X-17).

Thoracotomy, per se, results in elevation of the serum glutamic oxalacetic transaminase, presumably by release from damaged pectoral and intercostal muscles, and this must be taken into consideration in the evaluation of the test following major surgery.

Myocardial ischemia of 45 minutes duration seen in dog X-84 who failed to develop infarction after ligation of the left circumflex coronary artery did not result in increased transaminase activity. This is analogous to the usual absence of increased levels following angina pectoris and coronary insufficiency in man associated with reversible S-T and T-wave changes.

These problems are at present under further study.

The fact that the activity of the serum glutamic oxalacetic transaminase in infarcted muscle is only 2 to 10 per cent of that in the normal muscle of the same heart, together with the observation that the transaminase activity in infarcted muscle diminishes proportionately to the age of the infarct, strongly suggests that the mechanism of elevation of transaminase activity is simply one of release of the enzyme into the blood stream following death or increase in cellular membrane permeability. The routes of excretion and degradation of the enzyme are not yet known but are under study.

The spectrophotometric method of assay of serum glutamic oxalacetic transaminase is relatively simple, rapid, and inexpensive. In our hands its accuracy is highly reproducible, and we have used the method to investigate damage of heart and skeletal muscle and liver.[4, 7] It is apparent that a rise in transaminase activity is a useful index of the degree of necrosis of transaminase-rich tissue and does *not* in any way represent a nonspecific measurement of tissue inflammation.

Conclusions

Myocardial infarction due to ligation of coronary arteries in the dog is invariably followed by an increase in the serum glutamic oxalacetic transaminase activity.

The increase in activity occurs within six hours following ligation and both the degree and duration of enzyme abnormality appear to be proportional to the size of the infarct.

Myocardial ischemia of 45 minutes duration did not influence the serum level of glutamic oxalacetic transaminase.

Since the enzyme activity of infarcted muscle is only 2 to 10 per cent of that of normal muscle, the mechanism of elevation of transaminase activity is probably through release of the enzyme into the blood stream following an increase in the permeability of the injured heart muscle cell.

Acknowledgments

The authors wish to thank Dr. Arthur Allen for his generous assistance in carefully reviewing the pathologic material and Dr. Kathleen Roberts for her cooperation in contributing laboratory space. Dr. Albert Medwid devised the operative technic.

We are indebted for the technical help of Martin Podgainy, Alfred Friedman and Patricia Van Dawson.

Conclusiones in Interlingua

Infarcimento myocardiac causate per ligation del arterias coronari in canes es invariabilemente sequite per un augmento del activitate de transaminase oxalacetic glutamic in le sero.

Iste augmento occurre intra 6 horas post le ligation. Le grado e le duration del anormalitate enzymic pare esser proportional al dimensiones del infarcimento.

Ischemia myocardiac durante 45 minutas non influentia le nivello de transaminase.

Proque le activitate enzymic del musculo infarcite amonta a solo inter 2 e 10 pro cento del norma, le mechanismo del elevation in le activitate de transaminase depende probabilemente del augmentate permeabilitate cellular del musculo cardiac e un consequente disbuccamento del enzyma a in le fluxo sanguinee.

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Long-Acting Coronary Vasodilator Drugs: Metamine, Paveril, Nitroglyn and Peritrate

By Henry I. Russek, M.D., Burton L. Zohman, M.D., Alice E. Drumm, M.D., William Weingarten, M.D. and Virgil J. Dorset, M.D.

Recognition of the value of glyceryl trinitrate (nitroglycerine) in the treatment and prevention of anginal attacks has confirmed the belief that coronary blood flow may be influenced favorably by drug therapy and has led to a search for vasodilators capable of more prolonged action. The most popular of the newer agents which are alleged to have this desirable effect are Metamine, Paveril, Nitroglyn and Peritrate. In order to evaluate these drugs, the modifying action of each agent on the electrocardiographic response to standard exercise (Master two-step test) was recorded and compared in 21 carefully selected patients with coronary disease. Analysis of the results obtained with varying dosage administered from one to six hours prior to exercise disclosed that Peritrate was vastly superior to the other three drugs and that it alone was worthy of the designation "long-acting coronary vasodilator."

THE administration of nitroglycerine (glyceryl trinitrate) in the treatment of angina pectoris has long been recognized as the most effective measure for the relief of the acute attack. Although the drug is also unexcelled prophylactically when employed prior to contemplated exertion, the relatively short duration of its action obviously does not afford prolonged protection for the patient afflicted with this disease. For many years, therefore, the search has continued for a long acting coronary vasodilator which is capable of reducing the frequency and severity of anginal attacks by routine daily administration. Although numerous drugs have been characterized by their individual sponsors as fulfilling this need, few have been able to withstand the test of time and clinical usage. In previous studies[1-4] we have compared a number of "vasodilating" agents by recording their respective actions in modifying the electrocardiographic response to standard exercise (Master two-step test) in patients with coronary disease. The results of that investigation demonstrated that only papaverine (in large dosage) and pentaerythritol (Peritrate) tetranitrate exhibited prolonged effects which were similar to those observed for shorter periods with nitroglycerine. On the other hand, whiskey, aminophylline, Roniacol (beta-pyridylcarbinol tartrate), khellin (visammin), octyl nitrite, Priscoline (tolazoline hydrochloride), tetraethylammonium chloride, Paveril (dioxyline phosphate), heparin and Dicumarol (bishydroxycoumarin) were found to exert little or no influence on the exercise response.

At the present time a number of preparations are being widely employed because of claims that these agents are long-acting coronary vasodilator drugs. In each instance the manufacturer asserts that his drug "prevents anginal attacks or greatly diminishes their number and severity." The most popular of these agents in current usage are Metamine (triethanolamine trinitrate biphosphate), Paveril (dioxyline phosphate), Nitroglyn (glyceryl trinitrate in a sustained-action tablet) and Peritrate (pentaerythritol tetranitrate). Obviously, confirmation of these claims as well as measurement of the clinical response to each of these drugs is necessary to assess their relative value in

A joint project of the Cardiovascular Research Unit, Department of Medicine, United States Public Health Service Hospital, Staten Island, N. Y. and the National Heart Institute, United States Public Health Service, Washington, D. C., in conjunction with the Department of Medicine, Maimonides Hospital, State University, College of Medicine at New York City, Brooklyn, N. Y.

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therapy. The difficulty in determining the clinical effect of any agent in angina pectoris is well known to those engaged in the care of such patients. Inasmuch as the psychologic effects from placebo or other inactive drugs may significantly reduce "nitroglycerine requirements" and "frequency of attacks" whereas sedatives may accomplish a similar result by raising the pain threshold, a more reliable index of coronary insufficiency is needed than that afforded by the subjective sensation of pain.

In attempting to evaluate drugs which are alleged to have coronary vasodilator action we have been impressed with the objectivity of results obtained by means of a standard exercise test (Master two-step test) in carefully selected patients with coronary insufficiency.[1-4] By recording and comparing the ability of specific agents to modify the electrocardiographic response to exercise, drugs exerting favorable effect could readily be identified and the duration of their action measured. To have validity, such investigation must include only those patients with coronary disease who on repeated testing under identical conditions exhibit a relatively constant positive response to a given amount of exercise. By screening a large number of patients in anticipation of the present study, we selected 21 subjects in whom the necessary criteria were fulfilled.

Material and Method

All 21 of the patients in this series were men between the ages of 46 and 69 years. Nine of the group had sustained myocardial infarction and 15 presented classic symptoms of angina pectoris. Arterial hypertension was present in 9 of the 21 subjects. In all patients included in this series, the control response to exercise remained constant when recorded from day to day, and, in addition, could be modified favorably by the sublingual administration of therapeutic doses of nitroglycerine just before the test. By establishing this prerequisite, it was felt that a basis for comparison could be obtained between the effect of the known vasodilator, nitroglycerine, and that of other agents with unknown or undefined action. In each of the 21 patients Metamine (triethanolamine trinitrate biphosphate), Paveril (dioxyline phosphate), Nitroglyn (coated granules of glyceryl trinitrate) and Peritrate (pentaerythritol tetranitrate), respectively, were administered on different occasions from one to six hours before the performance of measured exercise. Medication was administered in varying dosage before breakfast in each instance. The results have been carefully recorded and compared.

Results

The 21 patients in this series performed 258 exercise tests following the administration of Metamine. The dosage employed was 2.0 to 6.0 mg. orally before breakfast. After taking the drug, exercise tests were obtained at variable intervals up to six hours but usually no more than three tests were performed in the individual case on any one day. A slight effect on exercise response was observed in only six cases in this series. In the remaining 15 patients, Metamine failed to exert a significant influence on the electrocardiograms recorded after standard exercise. Consequently, the modifying effect of this agent on exercise response must be regarded as relatively slight (figs. 1 through 4).

Paveril (dioxyline phosphate), the synthetic analogue of papaverine, when administered in doses of 200 to 500 mg., orally, showed a significant effect in only 6 of 21 patients tested. Moreover, even in those showing favorable response the duration but not the degree of electrocardiographic abnormality was modified favorably (figs. 1 through 4). In evaluating the drug 174 exercise tests were performed. Paveril appeared to be a much less potent drug than papaverine according to this method of testing.[4] Comparative studies revealed Paveril to be superior to Metamine but less effective than Nitroglyn or Peritrate (figs. 1 through 4).

In evaluating Nitroglyn, a preparation containing specially coated granules of glyceryl trinitrate (nitroglycerine), a dose of 2.4 to 9.6 mg. ($\frac{1}{25}$ to $\frac{4}{25}$ grain) was administered to 21 patients from one to six hours prior to the commencement of exercise. In these subjects 346 tests were performed following the administration of the drug. The dosage of 2.4 mg. ($\frac{1}{25}$ grain) was found ineffective up to six hours after its administration in all patients tested. Similarly in 8 of the 21 patients no effect was noted even with dosage levels

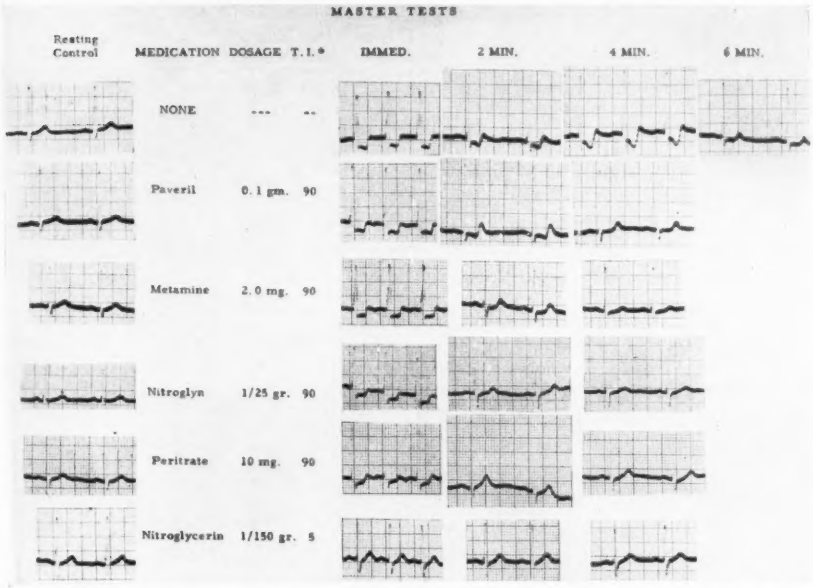

FIG. 1. Master test responses (lead V_4) obtained in a patient with angina pectoris with and without the administration of drugs.

* T.I., time interval (minutes) between medication and beginning of test.

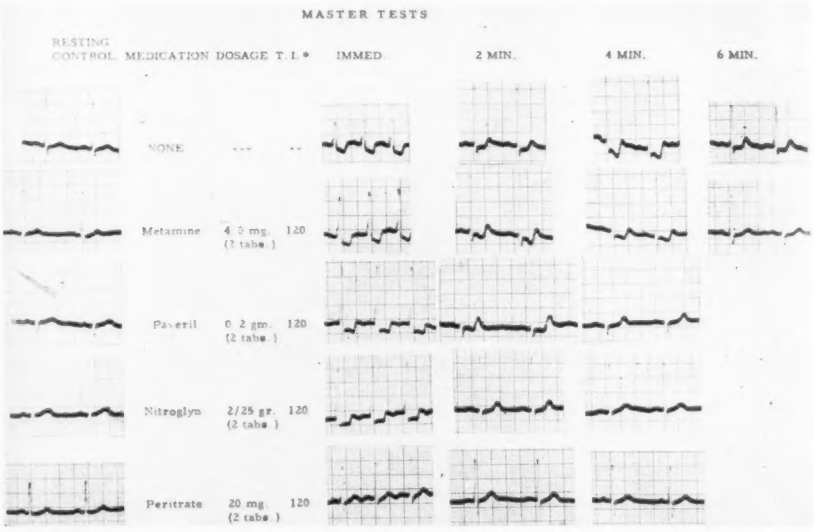

FIG. 2. Master test responses (lead V_4) obtained in a patient with angina pectoris with and without the administration of drugs.

* T.I., time interval (minutes) between medication and beginning of test.

as high as 9.6 mg. ($\frac{4}{25}$ grain). In the 13 remaining patients, however, slight to moderate improvement was observed in exercise response as long as six hours after the administration of 4.8 to 9.6 mg. ($\frac{2}{25}$ to $\frac{4}{25}$ grain) (figs. 1 through 4). In no instance did this sustained action preparation of nitroglycerine cause a normal exercise response to be recorded

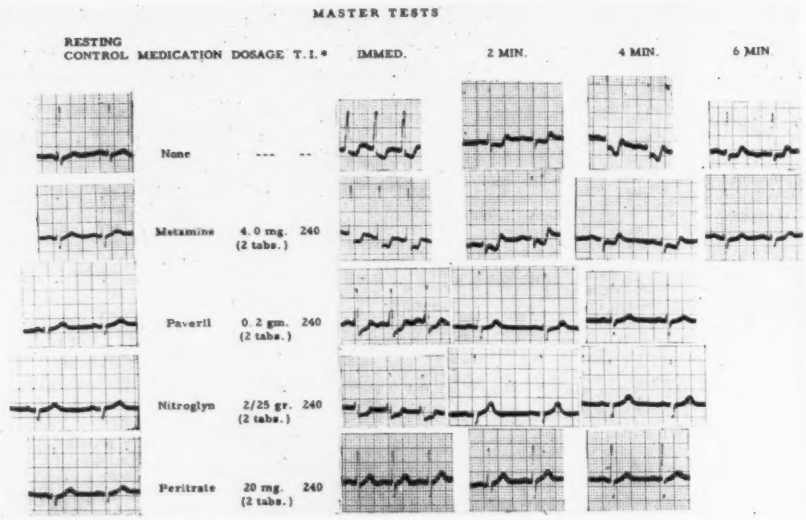

FIG. 3. Master tests (lead V_4) obtained in a patient with angina pectoris with and without the administration of drugs.

* T.I., time interval (minutes) between medication and beginning of test.

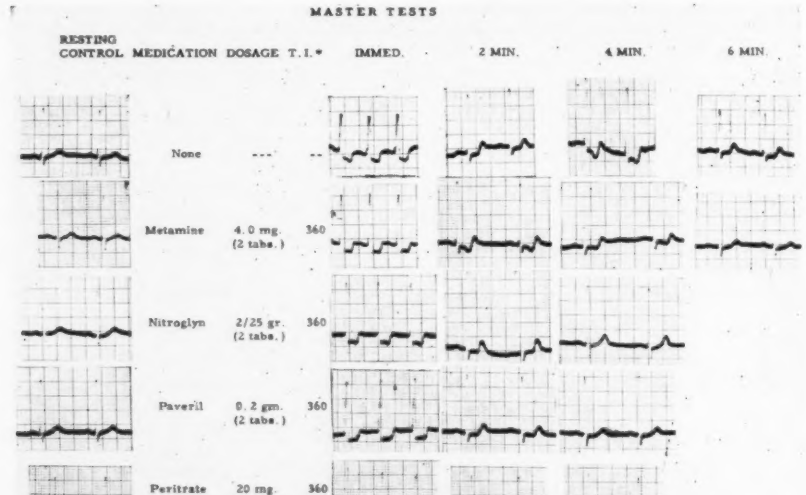

FIG. 4. Master test responses (lead V_4) obtained in a patient with angina pectoris with and without the administration of drugs.

* T.I., time interval (minutes) between medication and beginning of test.

even when massive dosage was employed. These findings are in distinct contrast with those observed with the sublingual preparation of the drug and with ordinary doses of Peritrate respectively (figs. 1 through 4).

Peritrate (pentaerythritol tetranitrate) was administered in a dose of 10 to 20 mg. to the 21 patients in this study. As with the other drugs the response to exercise was recorded at varying intervals up to six hours following

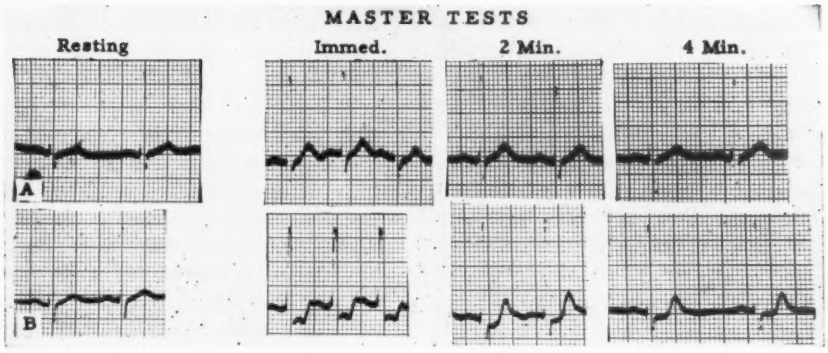

FIG. 5.*A*. Master test response 2 hours after 20 mg. Peritrate (taken before breakfast). *B*. Master test response 2 hours after 20 mg. Peritrate (taken after breakfast). Note markedly positive test in *B*.

its administration. A total of 230 exercise tests were performed in evaluating the effects of this agent. In a dose of 10 to 20 mg., Peritrate was found to exert a marked modifying influence on the electrocardiographic response to standard exercise in 14 of the 21 patients tested. In almost all of the subjects showing favorable response, the results were comparable to those obtained with glyceryl trinitrate but the duration of action was considerably more prolonged. Thus with Peritrate an improved response could be elicited as long as five hours or more after its administration (figs. 1 through 4). The importance of taking the drug with the stomach empty is shown in figure 5.

COMMENT

In previous studies it was found that papaverine in large oral dosage is an effective coronary vasodilator. The fact that this drug is still classified as a narcotic and is an expensive medicament when prescribed in optimum dosage (at least 0.2 Gm. or 3 grains three or four times a day) has greatly hindered its use in the treatment of angina pectoris. The introduction of Paveril, the synthetic analogue of papaverine, therefore, raised the hope that an effective substitute for the natural alkaloid was now at hand. Although Paveril has been reported from animal experiments to be a more potent coronary vasodilator than papaverine, our observations indicate that the synthetic preparation has a considerably weaker action in man than the opium derivative. Comparative studies to delineate the degree and duration of action of various drugs as measured by the two-step test have indeed shown little to commend the continued use of Paveril in the routine therapy of angina pectoris. Similarly, we have been unable to confirm the claims made for Metamine as a "long acting" coronary vasodilator.

The excellence of glyceryl trinitrate in the treatment of the acute attack and in prophylaxis just prior to contemplated exertion has for many years suggested its use in a preparation so designed as to permit slow and steady absorption for prolonged protection. Nitroglyn represents an admirable attempt to achieve this goal, but from our experience appears to fall far short of the mark. Even in large dosage the release of the drug must be too slow for satisfactory clinical response; as much as 9.6 mg. ($\frac{4}{25}$ grain) failed to modify the exercise response in some patients who reacted dramatically to 0.4 mg. ($\frac{1}{150}$ grain) of the ordinary hypodermic preparation sublingually. Nitroglyn in massive dosage did show, however, a slight to moderate effect on the exercise response during the six-hour period following its administration in almost two-thirds of the patients tested. Nevertheless, in no instance did this sustained action preparation cause a normal exercise response to be recorded, a result contrary to common experience with glyceryl trinitrate and Peritrate respectively.

The findings of this study indicate that of the four drugs tested only Peritrate, (penta-

erythritol tetranitrate) is worthy of the designation, "long-acting coronary vasodilator". In two-thirds of the patients tested, this drug (in 10 to 20 mg. doses) approximated the effects of glyceryl trinitrate (nitroglycerine) on the electrocardiographic response to exercise. Peritrate, moreover, exhibited its action up to five hours or more following administration, whereas the effect of nitroglycerine persisted for only 15 to 30 minutes. It is significant however, that in most cases Peritrate did not confer protection during the first hour following its administration. This lag in its activity was to be expected since even with massive doses of nitroglycerine taken orally (not sublingually) we have observed not only an attenuation of its effect but also a latent period of 30 minutes or longer before its action could be detected. It cannot be too strongly emphasized that Peritrate should not be taken after food but only when the stomach is empty, i.e. before meals. We have repeatedly found the total action of the drug to be lost when its ingestion followed the taking of food (fig. 5). Failure to recognize this fact may be responsible for differences in opinion regarding the efficacy of this and related drugs in the treatment of patients with angina pectoris. Peritrate appears to fill adequately the need for prolonged coronary vasodilatation in most patients with this disease.

Summary

Evaluation of vasodilator drugs in the treatment of angina pectoris continues to present a difficult problem because of the lack of objective methods of study, the element of subconscious bias on the part of both patient and physician and the unreliability of pain as a quantitative measure of underlying coronary insufficiency. It has been shown, however, that the ability of vasodilators to modify the electrocardiographic response to standard exercise (Master two-step test) in carefully selected patients provides a sound basis for assessing the relative and absolute value of each of such agents in the treatment of this disorder.

Employing this technic, a study of Paveril (dioxyline phosphate), Metamine (triethanolamine trinitrate biphosphate), Nitroglyn (coated granules of nitroglycerine) and Peritrate (pentaerythritol tetranitrate) was undertaken in 21 patients in whom control records obtained after standard exercise remained relatively constant from day to day. The results obtained with Metamine, Paveril and Nitroglyn were in sharp contrast with those observed after the administration of Peritrate. They may be summarized as follows:

1. Metamine produced little or no significant effect on exercise response as measured electrocardiographically in all patients in the series.

2. Paveril in some instances was mildly effective but its action was not sustained and its influence was never striking even with massive dosage. Only 6 of 21 patients showed significant improvement in exercise response following the use of this drug. Paveril does not appear to be as potent as papaverine in comparable dosage.

3. Nitroglyn, in spite of the logic behind its use, gave disappointing results. In the usual recommended dosage, 2.4 mg. ($\frac{1}{25}$ grain), the preparation appeared totally inert. With larger doses, 4.8 to 9.6 mg. ($\frac{2}{25}$ to $\frac{4}{25}$ grain), Nitroglyn evoked slight to moderate improvement in exercise response for a period of six hours following its administration in almost two-thirds of the patients tested. Nevertheless, the drug failed to induce a normal electrocardiographic response to exercise in any of the 21 patients in the series, a result far surpassed by the sublingual administration of nitroglycerine and by Peritrate, respectively.

4. Peritrate, in a dose of 10 to 20 mg., showed a marked modifying influence on the response to standard exercise in 14 of the 21 patients tested. The effect of this agent was comparable to that of nitroglycerine, but its action, after a latent period of 60 to 90 minutes, could be demonstrated as long as five to six hours after the administration of a therapeutic dose. Clinical response was markedly attenuated or totally abolished, however, when Peritrate was taken after food. Of the four drugs tested only this agent appears worthy of the designation "long-acting coronary vasodilator." Peritrate appears to satisfy the

need for prolonged coronary vasodilatation in most patients with angina pectoris.

Summario in Interlingua

Nos ha interprendite un studio de Paveril (phosphato de dioxylina), Metamina (triethanolamina-trinitrato-biphosphato), Nitroglyn (granulos incrustate de nitroglycerina), e Peritrato (tetranitrato de pentaerythritol) in 21 cautemente seligite patientes in qui registrationes de controlo post exercitio standard se habeva monstrate relativemente constante ab un die al altere. Le sequente es un summario de nostre constatationes:

1. Metamina produceva pauc o nulle significative effecto super le responsa post exercitio in le electrocardiogrammas de omne le patientes in iste serie.

2. In alicun casos Paveril se monstrava lavemente efficace, sed su action non durava e su influentia esseva nunquam frappante, mesmo post.

3. Nitroglyn—ben que su uso es supportate per considerationes logic—produceva resultatos disappunctante. In le dosage normalmente recommendate (2,4 mg.), le preparato se monstrava totalmente inerte. In dosages plus grande (4,8 a 9,6 mg.), illo provocav una leve o moderate melioration del responsa a exercitio durante un periodo de 6 horas post le administration in quasi duo tertios del patientes investigate.

4. Peritrato, administrate in un dosage de inter 10 e 20 mg, produceva un marcate modification del responsa post exercitio standard in 14 del 21 patientes investigate. La effecto de iste agente esseva comparabile al effecto de nitroglycerina, sed su action—post un latente periodo de inter 60 e 90 minutas—esseva demonstrabile usque a 5 o 6 horas post le administration de un dose therapeutic. Del altere latere, quando Peritrato esseva prendite post alimentos, le responsa clinic esseva marcatemente reducite o totalmente abolite.

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The Theory of Kent

A Histologic Study of the Normal Atrioventricular Communications of the Human Heart

By MAURICE LEV, M.D. AND RUTH LERNER, M.D.

This is an anatomic study of an alternate theory of conduction, first advanced by Kent, that conduction from atria to ventricles is by way of numerous muscular communications, rather than exclusively through the bundle of His. The entire atrioventricular rings of 22 fetal and newborn hearts, in addition to the A-V node, bundle and bundle branches in five adult hearts, were serially sectioned. No muscular communications outside the conduction system were found. Communications between the A-V node, bundle and left bundle branch with the ventricular musculature were frequently found in the fetus, and less commonly in the adult.

THE current conception of the initiation and conduction of the impulse in the human heart is as follows: The impulse is initiated in the sinoatrial (S-A) node, is spread through the atrial musculature to the auriculoventricular (A-V) node, then through the bundle of His and its arborizations. The purpose of this investigation is to evaluate the anatomic basis of an alternate theory first presented by Kent.[1] According to this theory, conduction from the atria to the ventricles is along several muscular pathways instead of exclusively through the bundle of His.

HISTORICAL REVIEW

In 1893, Kent[1] showed that in the newborn rat there are muscular connections between atria and ventricles, not only in the septum, but in the right and left lateral walls of the heart. In the young rabbit, such communications are found in the right lateral wall and the medial part of the left A-V ring, in addition to the septum. Similar connections are also found in the guinea pig and hedgehog. In the monkey, however, only here and there do muscular fibers pass from atria to ventricles. At about the same time, His[2] described the bundle named after him, and believed this to be the only communication between atria and ventricles. In 1913, Kent[3] described, in the human heart, a communication between the right atrium and ventricle, in the lateral aspect. In the following year,[4, 5] in this region, he described a right lateral auriculoventricular node of specialized tissue which communicated with both atrium and ventricle. When the anatomic connections between the left atrium and ventricle in a mammal were severed, and the section was carried through the septum, co-ordinated beats passed from atria to ventricles. He thus postulated that conduction persisted along the right lateral wall.[6] He then enlarged his concept to include conical neuromuscular structures present in the A-V rings, similar to neuromuscular spindles, which connected with both atria and ventricles.[7] Kent accordingly postulated that there are numerous pathways from atria to ventricles in the mammalian heart.

In the intervening and ensuing years, many workers looked for the communications of Kent. Their existence was denied by Tawara,[8] Keith and Flack,[9] Pace,[10] Blair and Davies,[11] and Kistin.[12] Communications outside the "conduction system" were, however, described by Retzer,[13] Todd,[14] and Glomset and Glomset.[15] No one, however, has confirmed the finding of a specific node in the right lateral wall, or neuromuscular spindles of the type described by Kent.

In addition, other communications between atria and ventricles within the conduction system have been described. Thus, Curran[16] described a connection between the A-V node and the septum in mammals, including man. This was denied by Blair and Davies, who found no direct connections between the A-V node and bundle and septum. Mahaim and his associates,[17-25] however, in a series of comprehensive serial-section studies, showed that in man, dog, sheep, calf, rabbit and cat, small connections are frequently present between the bundle of His and the origin of the left branch and the septum and, occasionally, between the A-V node and the septum. In the rabbit and cat, such connections are commonly found between the beginning of the right branch and septum, but this is never found in man.

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Several investigators have commented on atrioventricular communications in the embryo and fetus. In embryos less than 20 mm., Mall[22] (1912) found several communications between atria and ventricles outside the bundle of His. In one case, there was one in front and behind the left ostium, with several small ones in the right ostium. In another, he found two marked connections, one in front of each ostium. In the fetus, Robb, Kaylor and Turman[23] found connections outside the bundle of His, between atria and ventricles, in two fetal hearts. In addition, direct communication between the bundle and the right and left branches to the septum were present. According to these writers, the right outflow is not of one branch, but consists of several branches.

Extra atrioventricular communications have been described in abnormal hearts. Thus, in a cor biloculare, Mönckeberg,[24] found that the A-V bundle did not proceed into the ventricle. However, there was a bundle on the left side of the ostium, at the junction of the annulus fibrosus with the root of the aorta, anteriorly, connecting atrial musculature with the subendocardial ventricular musculature. In another case, the seat of patent foramen primum, transposition of the ventricles, origin of both arteries from the right ventricle, and pulmonary stenosis, there was an anterior accessory connection which joined with the A-V bundle to proceed into the ventricles. In four cases of Wolff-Parkinson-White syndrome, accessory bundles have been found. Thus, Öhnell[25] found a communication between the left atrium and ventricle, and Wood, Wolferth and Geckeler,[26] and Lev, Gibson and Miller[27] between the right atrium and ventricle, and Deerhake, Kimball, Burch and Henthorne,[28] between both atria and ventricles, in this type of anomalous conduction.

This review indicates that no definite statement can be made, at present, as to the presence or absence of accessory atrioventricular communications in the normal heart. Therefore, it is self evident that it is not known whether the accessory bundles found in pathologic states constitute abnormalities.

Material and Methods

Serial sections were cut throughout the entire A-V rings of 20 formalin-fixed fetal and newborn hearts, in addition to one 2-day-old and one 3-week-old heart. In 19 of these, the entire right and left A-V rings were divided into six blocks, and in three, these orifices were kept in one single block. Serial sections were cut at 10–12 microns. All sections were retained, and stained alternately with hematoxylin and eosin and Van Gieson stains. The age and technical details of these hearts are included in table 1.

Table 1.—*Technical Details of Fetal and Newborn Hearts Studied*

Case No.	Age	No. of Blocks	Thickness of Section	No. of Sections Cut	No. of Sections Lost
1) S-2048-52	4 months gestation	5	12 μ	2908	1
2) S-46-53	4 months gestation	Entire A-V Ring in 1 Block	12 μ	1136	1
3) S-123-53	4 months gestation	Entire A-V Ring in 1 Block	12 μ	1046	2
4) A-69-50	5 months gestation	5	12 μ	3402	5
5) A-52-C-50	5 months gestation	5	12 μ	3616	11
6) A-26-50	6 months gestation	5	10 μ	4520	11
7) A-16-50	6 months gestation	5	10 μ	5005	5
8) A-67-50	6 months gestation	5	12 μ	3421	10
9) A-68-50	6 months gestation	5	12 μ	4104	8
10) A-91-B-52	6 months gestation	5	12 μ	4140	6
11) A-72-50	7 months gestation	5	12 μ	4498	6
12) A-73-50	7 months gestation	5	12 μ	4477	3
13) A-4-51	8 months gestation	5	12 μ	3915	10
14) A-148-50	9 months gestation	5	10 μ	4450	11
15) A-96-49	9 months gestation	5	10 μ	5006	11
16) A-2-A-51	9 months gestation	5	10 μ	5885	55
17) A-12-BS-53	9 months gestation	5	12 μ	5838	4
18) A-36-53	9 months gestation	5	12 μ	5005	8
19) A-10-A-53	9 months gestation	5	12 μ	5917	11
20) A-88-AS-52	9 months gestation	5	12 μ	6136	7
21) A-2-53	2 days	5	12 μ	5303	1
22) A-75-53	3 weeks	Entire A-V Ring in 1 Block	12 μ	1866	5

TABLE 2.—*Technical Details of Adult Hearts Studied*

Case No.	Age	No. of Sections Cut	No. of Sections Lost
A-37-53	14	1914	1
A-46-A-53	20	2310	14
A-82-A-53	23	2514	6
A-57-53	24	2706	4
A-21-53	30	2122	1

In addition, the A-V node and bundle, and upper third of the bundle branches, were studied in five adult hearts with no pathologic change. They were cut in a manner described elsewhere,[29] and serially sectioned at 12 microns. All sections were retained and alternately stained with hematoxylin eosin and Weigert-Van Gieson stains. The age and technical details of these hearts are included in table 2.

OBSERVATIONS

No accessory communications between atria and ventricles outside the A-V node, bundle and bundle branches were found in any of the fetal and newborn hearts. The structures, probably considered by Kent to be nodes, are actually insertions of atrial musculature (fig. 1). In young fetal hearts, before the development of much collagen in the atrioventricular rings, there is a marked proximity of the atrial and ventricular musculature, but there is no communication between the two (fig. 2).

The observations on the direct communications between the A-V node, bundle and beginning of the bundle branches and the ventricular septum, are embodied in the accompanying table 3.

In the fetal heart, the central fibrous body is still relatively poor in collagen, although the amount increases considerably at 6 to 7 months. In the fetal heart, the terminal portion of the A-V node and the penetrating and branching portions of the bundle of His send numerous, wandering projections of nodal fibers into the central fibrous body and the pars membranacea. Some of these end blindly or rejoin the bundle. Others, however, grad-

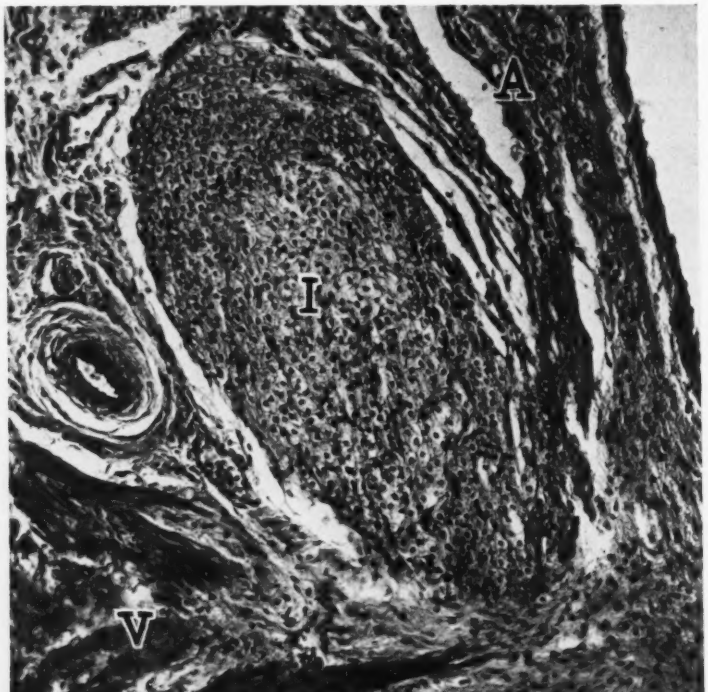

FIG. 1. Insertion of atrial muscle, possibly considered by Kent as specialized tissue. Heart of fetus of 6 months gestation. Hematoxylin-eosin stain. ×135. A—Atrial musculature. V—Ventricular musculature. I—Insertion of atrial musculature.

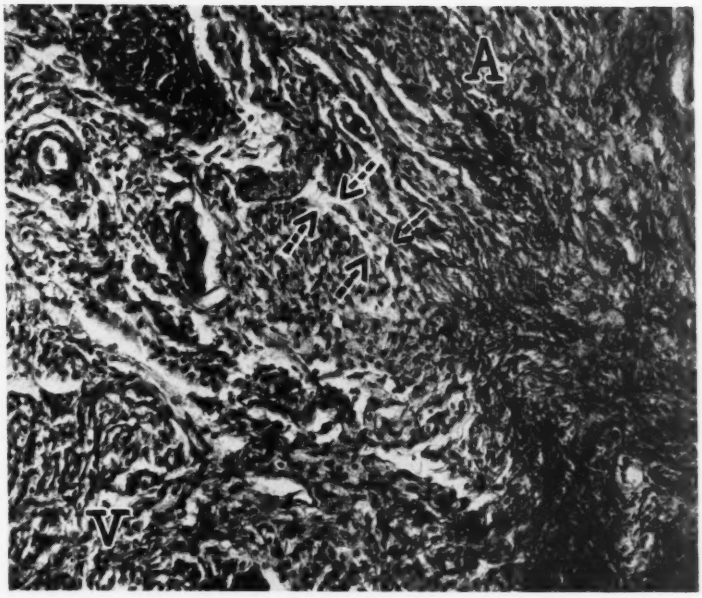

FIG. 2. Proximity of atrial and ventricular musculature. Heart of newborn. Van Gieson stain. ×135. A—Atrial musculature. V—Ventricular musculature. Arrows point to contiguity of atrial and ventricular musculature.

TABLE 3.—*Presence or Absence of Direct Communications Between the A-V Node, Bundle and Bundle Branches, and the Ventricular Musculature*

Case No.	Age	A-V Node to Ventricle	Junction of A-V Node and Bundle	Penetrating A-V Bundle to Ventricle	Branching A-V Bundle to Ventricle	Left Branch to Ventricle	Right Branch to Ventricle
S-2048-52	4 months gestation	0	+	+	0	+	0
S-46-53	4 months gestation	0	0	+	0	+	0
S-123-53	4 months gestation	+	+	+	+	+	0
A-69-50	5 months gestation	0	0	0	0	+	0
A-52-C-52	5 months gestation	0	+	0	+	+	0
A-26-50	6 months gestation	+	0	+	+	+	0
A-16-50	6 months gestation	0	0	0	+	+	0
A-67-50	6 months gestation	+	+	+	+	+	0
A-68-50	6 months gestation	+	0	0	+	0	0
A-91-B-52	6 months gestation	0	0	+	0	0	0
A-72-50	7 months gestation	0	0	0	0	0	0
A-73-50	7 months gestation	0	0	+	0	+	0
A-4-51	8 months gestation	0	0	+	0	+	0
A-148-50	Newborn	0	+	0	0	+	0
A-96-49	Newborn	0	+	0	0	0	0
A-2-A-51	Newborn	0	0	0	0	0	0
A-16-BS-53	Newborn	0	0	0	0	+	0
A-36-53	Newborn	0	0	0	0	0	0
A-10-A-53	Newborn	0	0	0	0	0	0
A-88-AS-52	Newborn	0	0	+	0	+	0
A-2-53	2 days	0	0	0	0	+	0
A-75-53	3 weeks	0	0	0	0	+	0
A-37-53	14	0	0	0	0	0	0
A-46-53	20	0	0	0	0	0	0
A-82-A-53	23	0	0	0	0	0	0
A-57-53	24	0	0	+	0	0	0
A-21-53	30	0	0	0	0	+	0

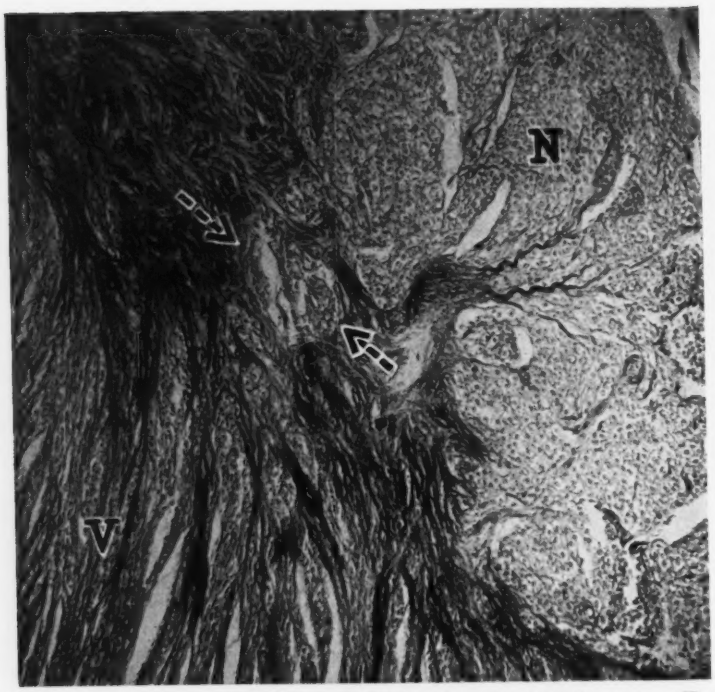

FIG. 3. Communication between terminal part of A-V node and ventricular septum. Heart of fetus of 6 months gestation. Van Gieson stain. ×135. N—A-V node. V—Ventricular musculature. Arrows point to the junction between the A-V node and the ventricular musculature.

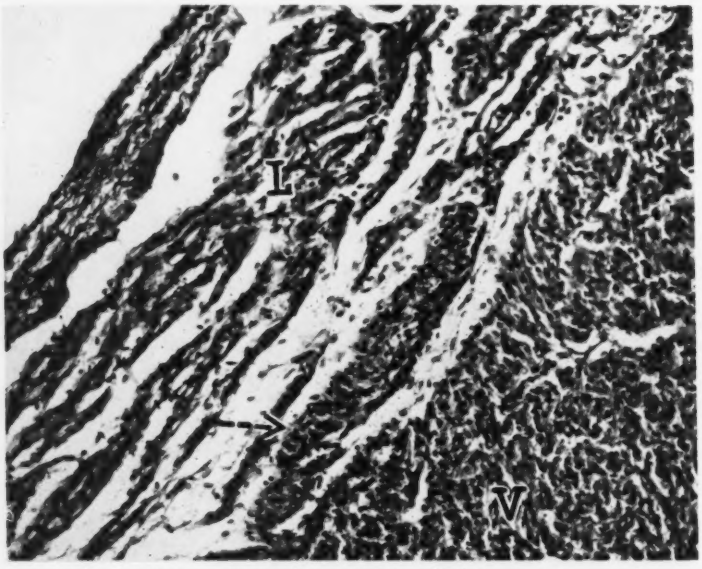

FIG. 4. Communication between beginning of left bundle branch and ventricular musculature. Heart of newborn. Hematoxylin-eosin stain. ×135. L—Left bundle branch. Arrow points to communication between left bundle branch and ventricular musculature.

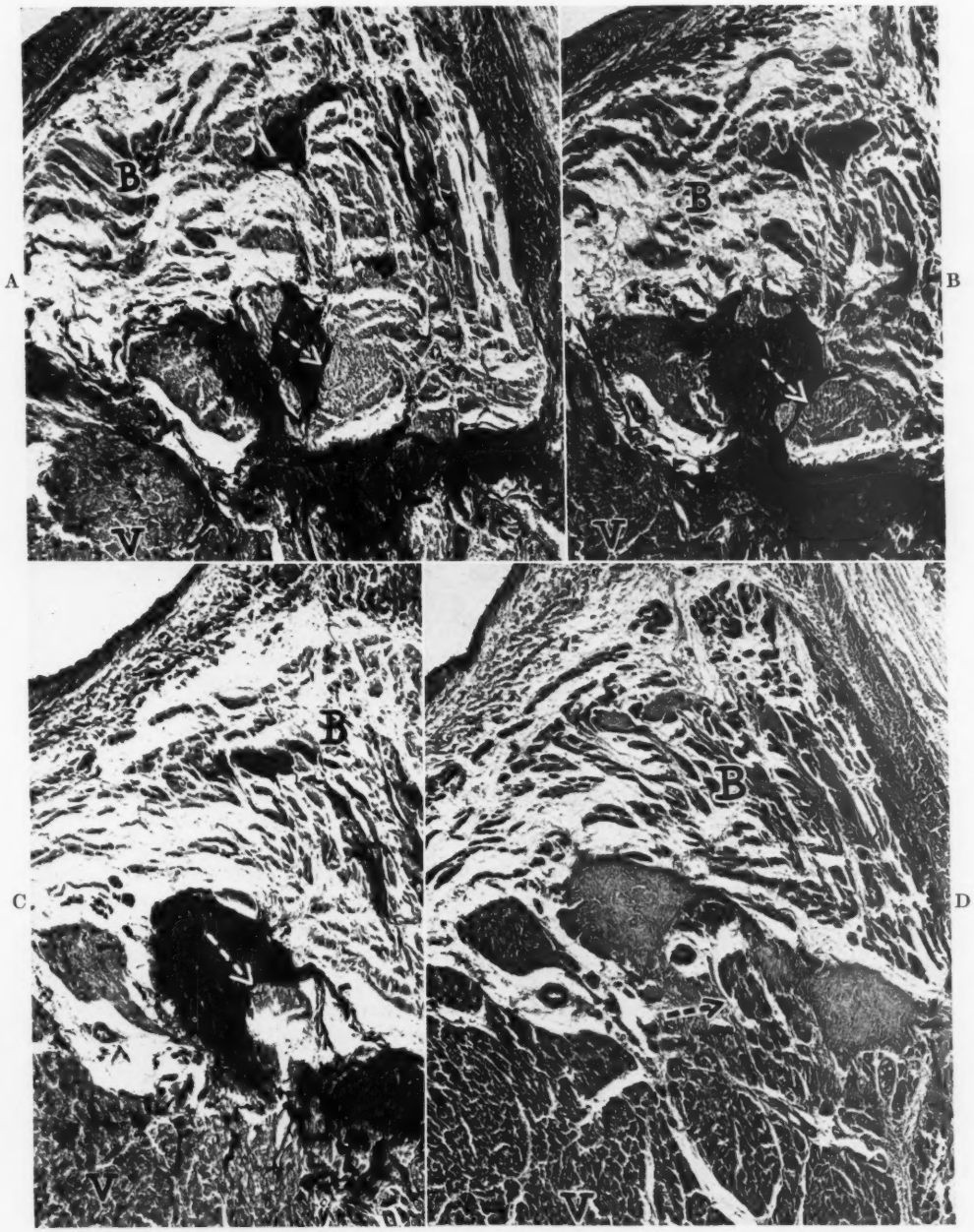

FIG. 5. Communication between branching portion of bundle of His and ventricular musculature. Heart of 24-year old female. (*A*, *B*, *C*) Weigert-Van Gieson stain. ×45. (*D*) Hematoxylin-eosin stain. ×45. B—Bundle of His. V—Ventricular musculature. Arrows point to communication between bundle and ventricular musculature in successive sections.

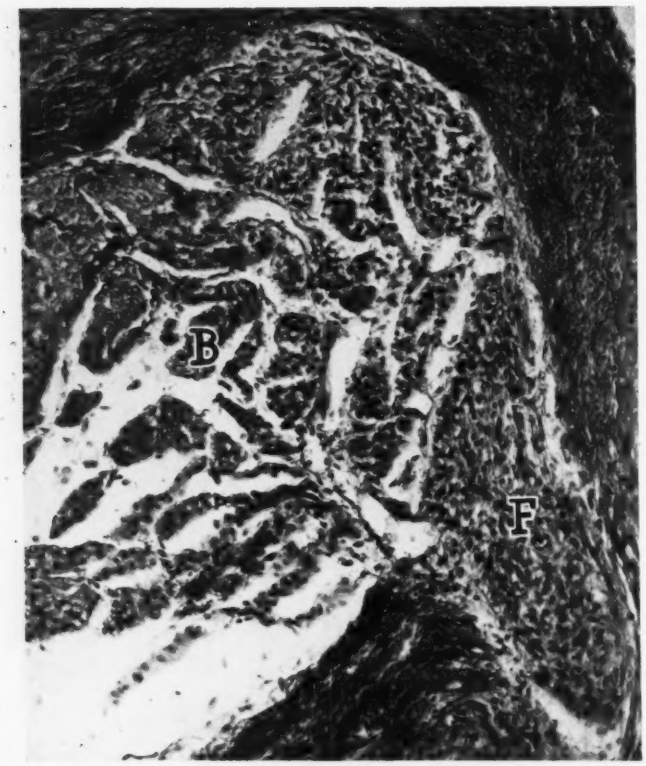

FIG. 6. False right bundle branch, which does not communicate with ventricular musculature. Heart of 3-week old infant. Van Gieson stain. ×135. B—Bundle of His. F—False right bundle branch.

ually fuse with the ventricular musculature (fig. 3.) The beginning of the left branch likewise sends fasciculi which rapidly terminate in the ventricular musculature (fig. 4). The size and number of these communicating fasciculi is greater in early, than in later, fetal life. At birth and neonatally, the A-V node communications become rare, while those of the A-V bundle and left bundle branch diminish (fig. 5). It is still common to see wandering fibers passing from the node, bundle and left branch, into the septum. They, however, terminate blindly, usually, without anastomosing with the ventricular musculature.

In the formation of the right bundle branch and its topography in the beginning of its course, considerable variation is found. The usual pattern is the giving off of one right branch which does not communicate with the septum until in the region of the muscle of Lancisi or distally. In one case, however, two right bundle branches were given off, with the first ending blindly (fig. 6). In another case, a single right branch bifurcated into two, and then the component parts rejoined to form one. In three cases, branches were given off from the beginning of the right bundle branch which entered the septum, but ended blindly without anastomosing with the ventricular myocardium. In no case was there a communication between the beginning of the right branch and the ventricular septum, as was commonly found in the beginning of the left branch.

DISCUSSION

This work indicates that normally there are no communications outside the "conduction system" between atria and ventricles in the human heart. There are no accessory nodes or neuromuscular spindles in the A-V rings, as

described by Kent. Small communications between the A-V node and bundle and left branch and ventricle are irregularly found, as described by Mahaim. The right bundle branch is a single trunk, but may show variation in its structure.

The theory of conduction in the mammalian heart must therefore be constructed on an anatomic base consisting of the S-A node, the atria, the A-V node, bundle and bundle branches, the communications present irregularly between the A-V node, bundle and beginning of left bundle with the ventricular myocardium (Mahaim's paraspecific fibers), the ventricular myocardium, and the nerve supply to the S-A and A-V nodes and to the atria and ventricles.

The presence of accessory bundles in the atrioventricular rings connecting atria and ventricles, in any heart, very likely constitutes a pathologic finding.

Conclusion

The entire atrioventricular rings, in addition to the A-V node, bundle and bundle branches, in 22 fetal and newborn hearts, were examined by serial section. This was supplemented by a serial section study of the A-V node, bundle and bundle branches, in five young adult hearts.

This study reveals that there are normally no accessory communications outside the "conduction system" between the atria and ventricles.

Mahaim's paraspecific fibers were routinely found in fetal hearts, less commonly in adult hearts.

Acknowledgment

Acknowledgement is made to Mr. Paul Marvan for his technical assistance.

Conclusion in Interlingua

In 22 cordes fetal e neonate, le nodos atrioventricular, le fasciculos e brancas fascicular, e in plus le integre anulo atrioventricular esseva examinate per sectiones serial. Isto esseva supplementate per un studio a sectiones serial del nodo atrioventricular e del fasciculos e brancas fascicular in cinque juvene cordes adulte.

Le studio indica que extra le "systema de conduction" il non existe normalmente ulle communication inter le atrios e le ventriculos.

Le fibras paraspecific de Mahaim esseva incontrate routinarimente in le cordes fetal, minus communmente in cordes adulte.

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Dissecting Aneurysm Produced by Diet

By WILLIAM B. BEAN, M.D. AND IGNACIO V. PONSETI, M.D.

Spontaneous dissecting aneurysm of the aorta in man is most commonly a sequel of hypertension but sometimes occurs in association with degenerative liquefaction of the media of the aorta. New light has been thrown upon dissecting aneurysm by its production in growing rats by a diet high in sweet peas. The offending agent has been isolated and a number of simpler related compounds have been synthesized and found effective. The relationship of this syndrome to a spontaneous dissecting aneurysm of the aorta in man is reviewed and some suggestions are made for investigation which may lead to newer methods of therapy.

Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the unusual law of nature by careful investigation of cases of rarer form of disease.—WILLIAM HARVEY.

DISSECTING ANEURYSM of the aorta is an uncommon disease of unknown cause. Arachnodactyly or Marfan's syndrome, an inherited mesodermal disorder, carries a high risk of dissecting aneurysm. Persons with coarctation and women during pregnancy have a high incidence of dissecting aneurysm. One variety is seen sometimes as a late complication of hypertension.

The experimental production of dissecting aneurysm of the aorta has been achieved previously by a variety of procedures which injure the vasa vasorum and the nutrition of the media. Many investigators have produced necrosis or degenerative changes in the aorta and larger arteries of rabbits by (1) crushing the vessel wall, (2) sheeting the vessel in wax, (3) dissecting off the adventitia and applying acids to the vessel wall.[1] Medial necrosis has been produced in dogs by repeated injections of histamine. In rabbits injections of epinephrine have been used to produce medial necrosis and dissecting aneurysms. Occasionally, in a rabbit fed very large amounts of cholesterol, dissecting aneurysms have appeared in conjunction with severely disorganizing atherosclerosis. More recently, Schlichter has produced dissecting aneurysm by direct thermocauterization of the adventitia producing coagulation necrosis with destruction of the vasa vasorum and with consequent degeneration of the media with liquefaction, cyst formation and collagen fiber replacement.[1, 2] All these experimental methods produced a nutritional disorganization by the mechanical interference with blood supply. At best they clarified the pathogenesis of only one form of dissecting aneurysm in man.

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STUDIES IN ANIMALS

New light has been thrown on this problem from an unexpected source by Ponseti and his co-workers.[3, 4, 5] Working on the problem of scoliosis and disease of cartilage matrix they induced experimental lathyrism in growing rats, with results which have promise of clarifying many seemingly unrelated clinical puzzles. Lathyrism has been known as a devastating disorder of men and domestic animals under certain conditions of famine or dietary fad when the food consists largely of legumes. The resulting disease is associated with weakness and spasticity, especially of the lower extremities. In severe cases urinary and fecal incontinence develop. The main features of the disorder Stockman reviewed in 1929.[6]

Geiger, Steenbock and Parsons[7] in 1933 noted scoliosis and hernias in white rats fed a diet made up of 50 per cent sweet pea seed. They found that a water extract of the seeds produced the same effect, whereas the extracted residue was not harmful when fed at the 50 per cent level. They did not mention any changes in the cardiovascular system. In

1934 Stockman[8] reported that a water extract of lathyrus peas produced a toxic effect on the brain and spinal cord of experimental animals. Again in 1948 Lewis and coworkers[9] observed spinal curvatures in rats fed various kinds of legumes. Vivanco and Jiménez Diaz[10] in Spain observed patients with legume intoxication who had lameness of the legs, similar to the lesions observed in rats fed a diet with large amounts of pea meal. Denny-Brown has reviewed the problem of lathyrism in connection with nutritional neuropathies.[11] In none of these studies, clinical or experimental, was there any mention of arterial lesions or of dissecting aneurysm. It may have been passed by as a nuisance which caused the death of many experimental animals which, otherwise, would have developed the expected lesions of the skeleton, nerves and connective tissue.

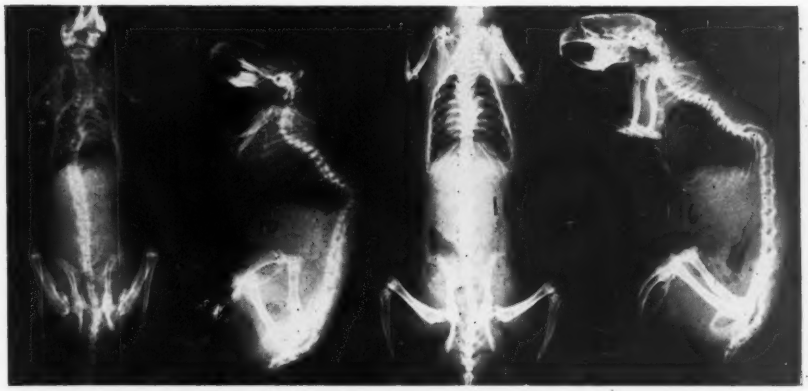
The present series of investigation was ushered in by Ponseti and Baird who verified and considerably extended the previous observations. In particular they called attention to the high incidence of aortic dissecting aneurysm which took a severe toll in the growing rats on the experimental diet.

Their first studies were as follows. They divided four weeks-old male rats of the Sprague-Dawley strain into three groups. To one group they gave a diet consisting of 50 per cent sweet pea meal, 28 per cent corn starch, 6 per cent sucrose, 4 per cent salt mixture, 10 per cent dried yeast, 2 per cent corn oil to which was added 0.2 cc. of halibut liver oil for each 100 Gm. of ration. Another group got the same diet to which 10 per cent casein was added and the third group had the further addition of 0.75 per cent methionine. Each week the rats were weighed and x-ray films were taken with the rats anesthetized with ether. At the end of three weeks of this program the skeleton first showed signs of demineralization, and then, or a little later, periosteal new bone was formed, especially at the level of the femoral metaphysis. Progressive bowing and deformity of the long bones followed. The animals soon appeared thin and listless with rumpled unkempt fur. Between the fourth and sixth weeks the intervertebral spaces narrowed irregularly with a tendency for the cephalad vertebra to slip forward over the caudal vertebra at the level of the changes in the intervertebral discs. About a week later collapse of two or three vertebral bodies resulted in kyphosis, and this in turn was followed by lateral slipping and vertebral rotation. Similar changes occurred in the mid-thoracic region two or three weeks later, resulting in typical kyphoscoliosis. The ribs became deformed because of the rotation of the thoracic vertebrae. All rats on the various experimental programs developed progressive scoliosis. Its severity was related to the duration of the experimental diet. If, after the scoliosis was well developed, the diet was changed to a stock diet, the long bones straightened, periosteal new bone disappeared, and the kyphoscoliosis became arrested. (fig. 1.)

Rats with additional casein and additional casein and methionine, grew much more rapidly, but the roentgenographic changes appeared earlier.

Thirty-eight to 75 per cent of the rats in different experiments died spontaneously of dissecting aneurysm of the aorta during the fifth to the ninth week. They had irregular, scattered medial necrosis throughout the thoracic aorta with extensive dissection where the fibers of the media were split by the passage of blood. Dissection continued out into the adventitia with the formation of large hematoma and rupture into the thorax. One animal had a large sacular aneurysm communicating with the lumen of the aorta by a wide opening. The media ended abruptly at this point and the intima was not distinguishable from the lining of the aneurysm. The wall of the aneurysm was formed by a thick layer of laminated clot and compressed adventitia.

In later experiments animals dying or sacrificed at various intervals had the following changes in the vertebrae and long bones. The epiphyseal plates appeared widened and distorted (fig. 2). The cartilagenous matrix lost its cohesion and there was loosening of the tendinous and ligamentous insertions. Epiphyseal slipping occurred. The endochondral ossification did not appear abnormal at first. Extensive subperiosteal new bone formation occurred in the metaphyseal region of the long bones. The intervertebral discs appeared



A *B* *C* *D*

FIG. 1. *A and B*, roentgenograms of a 10-week-old rat fed the 50 per cent sweet pea diet since 4 weeks of age. The shoulders are dislocated, there is kyphoscoliosis, and abundant new bone is being formed around both femurs. *C and D*, roentgenograms of the same rat taken at 16 weeks of age. At 10 weeks of age the diet was changed to the regular stock diet. The skeleton is better ossified than in *A* and *B* and the extraneous bone around the femurs has disappeared. The kyphoscoliosis has not changed but the sternum, which was deformed in *A* and *B*, is straighter.

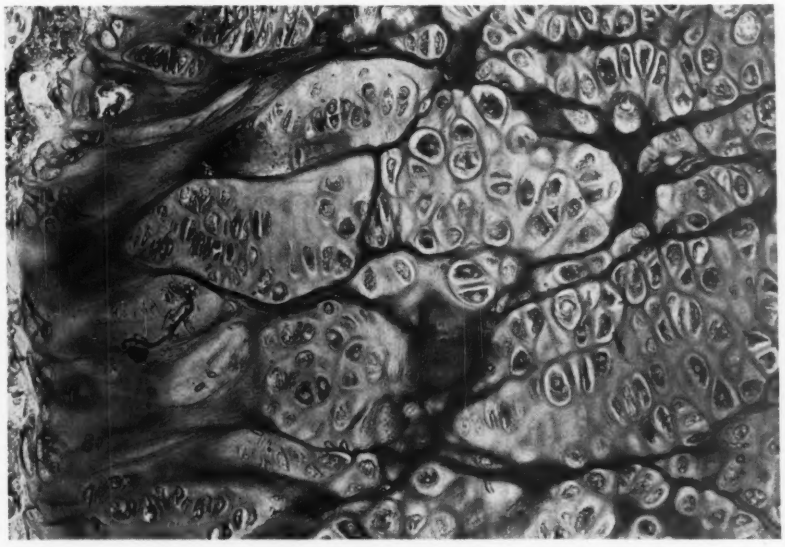
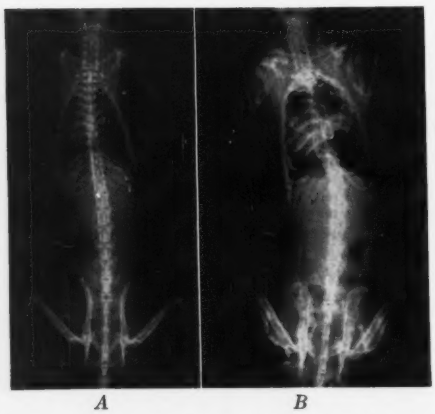


FIG. 2. Photomicrograph of the upper tibial epiphyseal plate of a 6-week-old rat which had been fed the 50 per cent sweet pea diet for three weeks. The clumped cartilage cells are separated by septa of metachromatic, fibrillated, cartilage matrix (Toluidine blue stain).

normal in the young animals. In some rats there were severe slippings of the vertebral epiphysis with compression and even severance of the spinal cord. In animals with compression of the spinal cord there was great distortion of the posterior funiculi and gray matter. In later stages the intervertebral discs were greatly distorted and narrowed. Degenerative arthritis was observed in many experimental animals.

In other experiments when the pea meal diet was fed to fully grown rats the cortical bone grew very thick (fig. 3). Histologic sections revealed dense bone with mosaic patterns



A B

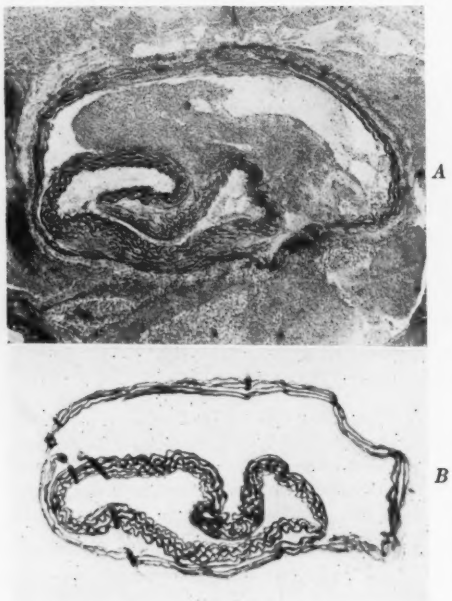
FIG. 3. *A*, roentgenogram of a 187-day-old rat fed the control diet. *B*, roentgenogram of the same rat fed the 50 per cent sweet pea diet for 198 days. Extensive new bone formation can be seen along the humeral and femoral diaphysis. The iliac bones are wide. No scoliosis developed as the rat was old when the pea diet was started.

and thick trabeculae resembling the bone seen in Paget's disease in man.

In all animals the bone changes antedated the muscle spasticity and the unsteady jerking gait which commonly occurred, presumably because of the periosteal detachments, slipped epiphyses and degenerative arthritis, and spinal cord lesions produced by the deformed spine. Muscles looked normal microscopically but they had a significantly higher oxygen utilization than the muscle of normal control animals.[4]

Scrotal and ventral hernias occurred in many of the affected animals, a disorder not seen in normal control animals of this strain. Electron microscope studies of the fibers of the tail tendon revealed nothing abnormal in the structure of the collagen fibers. Hernias appeared to be a result of a defect of ground substance rather than of collagen fibers.

The occurrence of dissecting aneurysm of the aorta was related to the age of the rat when the diet was started. In several groups of 22 and 23 day old rats, dissecting aneurysms occurred in anywhere from 38 to 75 per cent of the animals. Deaths from the aortic lesions occurred as early as 12 days after starting the diet. No aneurysms were produced when



A

B

FIG. 4. Dissecting aneurysm of the upper thoracic aorta. The rat died at 34 days of age, having been fed the 50 per cent sweet pea diet for 12 days. There was bilateral hemothorax. *A*, Hematoxylin and eosin stain. *B*, Orcein stain for elastic fibers. These fibers are well preserved.

feeding the pea meal diet was started later than the age of 51 days.

Dissecting aneurysms occurred in the ascending portion and the arch of the thoracic aorta. None was observed in the abdominal aorta. The lesions started in the media. The elastic and the muscle fibers did not appear abnormal at first. There was a loss of cohesion of fibers seemingly due to a defect of the binding power of the ground substance. Then patchy necrosis occurred in the smooth muscle cells. The elastic fibers remained unaltered. The intima ruptured at the site of the weakening of the media. Blood penetrated and dissected along the degenerated areas. The adventitia usually ruptured and the blood produced hemothorax or hemopericardium (figs. 4 and 5). In some of the young rats sacrificed two or three weeks after beginning the diet, dissecting aneurysms were smaller and had not ruptured. There was an attempt at repair with very cellular connective tissue patching the defect in the arterial

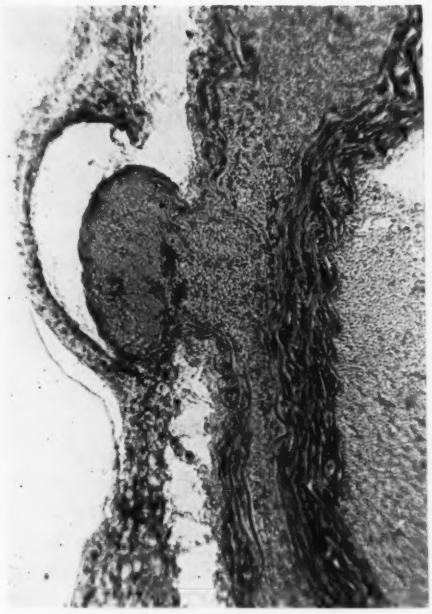


FIG. 5. Dissecting aneurysm of the arch of the aorta in a 45-day-old rat fed the 50 per cent sweet pea diet for 22 days. The adventitia bulges just prior to its rupture. Hematoxylin and eosin stain.

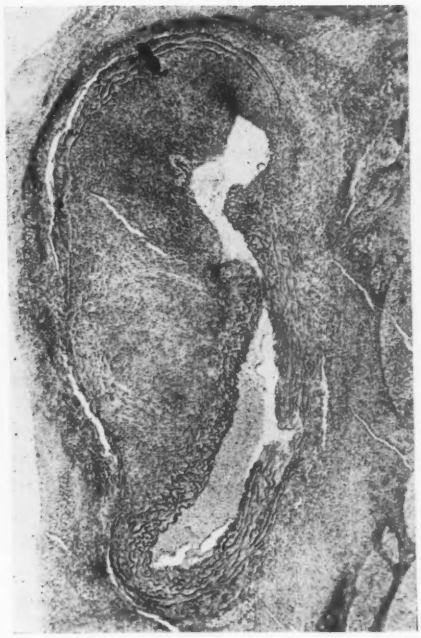


FIG. 6. Photomicrograph of the mid-thoracic aorta of a 36-day-old rat fed the 50 per cent sweet pea diet for 13 days. Very cellular connective tissue is seen in the media in an apparent attempt to patch up the defect of the arterial wall. Hematoxylin and eosin stain.

wall (fig. 6). No lesions were observed in the smaller arteries, veins or the capillaries.

No abnormalities were observed in the lungs, liver, spleen or kidney. Two rats kept on the diet for 216 days developed testicular abnormalities with arrest of spermatogenesis, sloughing of cells and giant cell formation. There were no special changes in the other endocrine glands.

Testosterone and vitamin B_{12} singly or together did not protect. The substitution of cotton seed oil or cod liver oil made no difference. It was impossible to prevent the development of the lesions by large doses of vitamin E.

Presumably all these lesions occurring under the experimental conditions result from a similar process. They all occurred in areas where the ground substance contains chondroitin sulfate as the chief or sometimes only mucopolysaccharide. All the lesions encountered in the experimental animals could be a result of defective formation or excessive destruction of chondroitin sulfate in the ground substance.

So-called idiopathic scoliosis in man usually begins before puberty. The deformity ceases to progress as soon as the skeletal growth of the spine is completed and the epiphyseal plates become obliterated. Radiograms indicate that patients with rapidly progressing scoliosis have defects in the vertebrae particularly in the areas adjacent to the cartilaginous plates. The deformity is worse when the mid thoracic vertebrae are involved. Childhood diseases, such as rickets, which produce weakening of the epiphyseal plate do not lead to scoliosis presumably because there is no weakening of the ligamentous insertions.

STUDIES IN MAN

On the basis of these striking demonstrations by Ponseti and associates we reviewed our clinical experience with patients with dissecting aneurysm who had come to autopsy. Of 27 records available in the files of the Department

of Pathology there were 20 with x-ray films, or a description of the skeleton detailed enough to establish whether there had been any significant deformity. Seven, or 35 per cent, had gross abnormalities. Five had deforming kyphoscoliosis and two had severe pigeon breast deformity. In so small a group chance may have had some effects; and there are too few cases for statistical treatment. In an effort to get some group for comparison, we selected autopsied patients who had had hypertension during the same period, selected to match the age and sex of those with dissecting aneurysm, and a random selection of similar patients admitted to the Medical Service during the past six years. In 100 adequate autopsy records and in 500 medical admissions the incidence of a significant kyphoscoliosis was not over 2 per cent. Such comparisons are suggestive only and we need a clinical study to search for correlations along these lines.

These observations must not lead us to underrate the commonest clinical basis for dissecting aneurysm which still remains hypertension with sclerosing lesions of the small nutrient arteries of the media. There is a group of persons, however, without hypertension or much arteriosclerosis, in whom a metabolic flaw in production or maintenance of ground substance produces widespread disorders of the body's supporting matrix of binding material. They have a high incidence of deforming weakness of the bony skeleton and more than the chance frequency of dissecting aneurysm. Casual comments on kyphosis and other bone deformities with dissecting aneurysms are found in Shennan's monograph[12] and elsewhere.[13]

Other Conditions in Which Dissecting Aneurysm is Common

Marfan's syndrome is a mesodermal defect with a variety of deformities occurring separately or in combination.[14] During the past decade it has become apparent that cardiovascular anomalies in Marfan's syndrome are very frequently the cause of death. In reviewing a series of 37 published autopsied cases, including all of those currently available, in 41 per cent there has been dissecting aneurysm of the aorta.[15] If one adds to this figure the number with cystic necrosis of the media or with fusiform or saccular nondissecting aneurysm of the aorta, more than 50 per cent were affected. The microscopic appearance of the lesion is quite regular. The elastic muscle fibers are deficient and replaced by loose collagenous fibrous tissue. The lesion is indistinguishable from the medial necrosis first described by Erdheim as a cause of dissecting aneurysm. Lesions of the heart valves commonly mistaken for those of rheumatic fever have been found in a number of instances but microscopic examination generally does not confirm the diagnosis of rheumatic heart disease. An explanation for the fundamental abnormality in Marfan's syndrome is obscure. Many of the suggestions of some endocrine abnormality are far from convincing. Sloper and Storey[16] have suggested that the disturbance in ground substance seen in the aorta might be responsible for such diverse lesions as the loose joints, the dislocation of the optic lens and perhaps even a disturbance of ossification of bone. Histologic studies of the ligaments and of the bones are not available from any autopsy report of Marfan's syndrome.

There are a number of other and miscellaneous suggestions that hormonal and endocrine disorders affecting the ground substance may be responsible for the occurrence of dissecting aneurysm. For instance in 1940 Kuntz and Hemplemann[17] reported three patients who had hypertension and who developed dissecting aneurysm following total thyroidectomy as a paliative measure for the treatment of hypertension. They suspected that the observed mucoid degeneration of the media was related specifically to the metabolic disturbance following the removal of thyroid activity.

A curious clinical feature of dissecting aneurysm is its frequency in pregnant women, particularly towards term. Indeed this has been reported in at least one woman who had arachnodactyly. It has been suggested that the general relaxation of pelvic joints, the depolymerization of ground substance of the symphysis and other similar changes in pregnancy may all be related to the same sort of

disorder of ground substance which has given rise to spontaneous dissecting aneurysm.

A final situation in which dissecting aneurysm may occur with undue prevalence is coarctation of the aorta. In this condition, however, a combination of the changes associated with hypertension, reducing the blood flow through the vasa vasorum and the mechanical disorganization of the coats of the aorta associated with the lesion of coarctation itself are adequate to explain the high incidence of dissecting aneurysm. No defect of ground substance has been found in this condition.

Discussion

We have presented the outlines of the story of how new understanding has come to the problem of clinical dissecting aneurysm in man from the improbable vantage point of research on bone lesions. The facts are simple. A diet high in legumes produces a variety of lesions in growing rats. All the lesions have as their basis a fault in the ground substance, the glue which holds the frame together. A number of workers have pushed the problem ahead and it is now established that β-aminopropionitrile, a simple chemical compound, is the toxic substance in peas which produces the lesions.

Such a compound presumably acts as an antimetabolite. Efforts are being made to find some related compound which by neutralizing or blocking its action might be called an antiantimetabolite. The structural resemblance of B-aminopropionitrile and pantothenic acid suggests a possible analogy with the disorder produced in human subjects by a pantothenic-acid-free diet and omega-methylpantothenic acid.[18]

Dissecting aneurysm in man has been recognized as a usually fatal complication in a few instances of hypertension and arteriosclerosis, in many persons with Marfan's syndrome, occasionally in pregnancy and coarctation of the aorta, and rarely in myxedema with hypertension. Another variety, mysterious in etiology, is caused by a dissolution of the aortic media with cystic degeneration. This last kind we have found in association with a very high frequency of deforming skeletal disease, notably "idiopathic" kyphoscoliosis. We suggest, but have not demonstrated, that this represents a widespread disorder of ground substance, probably an inborn error of metabolism, perhaps from a dietary lack, possibly from a toxic factor in food though this is the merest guess. A clue to one possible cause has been found in the series of brilliant studies which culminated in isolating a simple chemical compound which in low concentration can produce a disorder of ground substance in growing rats.

Marfan's syndrome, an inherited mesodermal defect with general characteristics of an entirely different order, may represent a genetically conditioned flaw in the integrity of ground substance as well as in mesodermal tissues. It is possible that part of the mechanism giving rise to its multiple deformities is related to the mechanism which destroys the patterned growth of rats. For the present the differences are more striking than the similarities.

We have no clear idea of how the general tissue softenings of pregnancy, or the myxomatous changes of hypothyroidism are related to the experimental lesion in rats. We do not know that they have any relation.

Summary

Taking the hint from clinical lathyrism, studies directed towards the elucidation of kyphoscoliosis have disclosed the fact that multiple lesions can be produced in growing rats by feeding small amounts of such simple chemical compounds as B-aminopropionitrile and aminoacetonitrile. The basic trouble is a ground substance disorder causing bone matrix failure, hernias and dissecting aneurysm. Searching for clinical correlates, we found a high frequency of skeletal deformities in persons who died of dissecting aneurysm.

As speculation we suggest that many, but by no means all, dissecting aneurysms arise from a failure of the ground substance to fulfill its natural function of holding things together. It may represent a genetic, metabolic or dietary fault. We suggest that some form of Marfan's syndrome may consist of a related but not identical dysfunction, an inborn error, genetically transmitted.

An experimental attack on fundamental

mechanisms now lies before us. Cardiologists may be grateful for light cast on any dark area and congratulate their orthopedic colleagues on an unexpected assist.

Summario in Interlingua

Inspirate per methodos previemente usate in le investigation de lathyrismo clinic, nos ha succedite a avantiar nostre effortios a elucidar le essentia de cyphoscoliosis usque al constatation que multiple lesiones pote esser producite in rattos crescente per un alimentation a parve quantitates de simple compositos chimic del typo de B-aminopropionitrilo o aminoacetonitrilo. Le disordine fundamental involve le substantia basal e causa secundarimente dysfunctionamento in le matrice ossee, hernias, e aneurysma dissecante. In nostre cerca de correlatos clinic nos trovava un alte frequentia de deformitates skeletal in personas qui habeva morite de aneurysma dissecante.

Speculativemente nos postula le theoria que multe aneurysmas dissecante—sed certo non omnes—resulta del facto que le substantia basal non exerce su function natural de mantener un coherentia general. Le vitio in le situation pote esser de natura genetic, metabolic, o dietari. Nos opina que certe formas del syndrome de Marfan consiste possibilemente de un dysfunctionamento affin, ben que non identic, i.e. un falta innate que es geneticamente transmittite.

Nos nunc nos trova confrontate con le problema de organisar un attacco experimental super le area del mechanismos fundamental.

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Cholesterol Pericarditis

Successful Treatment by Pericardiectomy

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Although cholesterol pericarditis is usually associated with myxedema, it may occur as a result of tuberculous infection or hemopericardium. Cardiac constriction is apparently an uncommon feature of the condition. A case of chronic constrictive cholesterol pericarditis was treated by pericardiectomy with complete relief of symptoms. Neither bacteriologic nor histologic studies of the resected pericardium revealed the etiologic basis for cholesterol accumulation within the pericardial sac.

CHOLESTEROL PERICARDITIS is a rare condition and usually occurs in association with myxedema. The first instance of pericardial effusion with large quantities of cholesterol was reported by Alexander[1] in 1919. This fluid contained 0.61 Gm. of cholesterol per liter and had a "gold paint" appearance. Although Alexander recognized that the patient was myxedematous, he did not associate the pericarditis with this condition. The occurrence of pericardial effusion in patients with myxedema was subsequently emphasized by Gordon[2] and others. In the case reported by Harrell and Johnston,[3] the serum cholesterol was 270 mg. per 100 cc. and the cholesterol content of the pericardial fluid 92 mg. per 100 cc. Bullrich and associates[4] found that the pericardial fluid from a patient with myxedema contained slightly more cholesterol than the blood. In 1946 Howard[5] reported the necropsy findings of a patient with myxedema. The pericardium contained 4000 cc. of dark, green fluorescent fluid in which were bright, sparkling yellow cholesterol crystals. Chemical examination of the fluid revealed a cholesterol content of 76 mg. per 100 cc. The pericardial fluid from five patients with myxedema was examined by Bustamente and Perez-Stable[6] and cholesterol was found in all, but in quantities much below the blood levels. In the case of cholesterol pericarditis reported by Merrill[7] the etiology was obscure although the clinical manifestations and the patient's response to thyroid extract suggested hypothyroidism.

Other conditions besides myxedema have been reported to be of significance in the production of cholesterol pericarditis. Tuberculosis has been suggested by Daniel and Puder[8] as an etiologic factor on the basis of the necropsy findings in one case. They postulated that hemopericardium may have occurred as a result of tuberculous involvement of the pericardium. Subsequent hemolysis of erythrocytes and absorption of a portion of the fluid accounted for the high cholesterol content of the pericardial fluid.

In a case of hemorrhagic pericarditis described by Voldet,[9] microscopic examination of the epicardium revealed numerous collections of cholesterol crystals surrounded by giant cells.

In 1950 Ada[10] reported a case of cholesterol pericarditis proved by biopsy and without demonstrable etiology. The pericardial fluid was golden yellow, opalescent, and contained 120 mg. of cholesterol per 100 cc. The blood cholesterol was 167 mg. per 100 cc. At thoracotomy several cholesterol plaques were noted on both the visceral and parietal pericardial surfaces. Since there was no evidence of cardiac constriction, only a biopsy was done. Microscopic examination revealed fibrous tissue containing masses of cholesterol, large numbers of foreign body giant cells and some regenerating fat cells.

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Recently we have treated a patient with chronic pericardial effusion of unknown etiology that progressed to constrictive pericarditis. Pericardiectomy was performed with complete relief of symptoms. Histologically, the resected pericardium revealed chronic cholesterol pericarditis. Because of the apparent rarity of this condition and since no reports of pericardiectomy for cholesterol pericarditis have appeared, this case is recorded in some detail.

Case Report

J. O. S., a 32 year-old white man, was admitted to the Houston Veterans Administration Hospital on Aug. 28, 1953 with the history of having been in good health until April, 1952, when he rather abruptly developed constant, dull, aching precordial pain and a sensation of fullness and tenderness in the epigastrium. The pain was markedly accentuated on deep inspiration. He had no other symptoms and the pain subsided within a short time. He was then well until the end of May, 1952, when similar symptoms recurred and he noted a temperature elevation to 102 F. At that time in a local hospital, his physician noted enlargement of the cardiac silhouette on fluoroscopy. On June 7, 1952 he was referred to another hospital where he remained for three weeks.

Physical examination at that time revealed a normal temperature, blood pressure of 116/76 and pulse rate of 72 beats per minute. There was enlargement of the area of cardiac dullness to the right and left. The heart sounds were faint, and no murmurs or thrills were noted. The lung fields were clear. The remainder of the physical examination was not remarkable. Laboratory studies revealed an erythrocyte count of 3,820,000, hemoglobin of 11.3 Gm. per 100 cc., hematocrit of 42 per cent and erythrocyte sedimentation rate of 36 mm. in 1 hour. The venous pressure was 16 cm. of saline and the circulation time, arm to tongue, was 30 seconds (Decholin).

On June 11, 1952, pericardial aspiration yielded 20 cc. of deep yellow fluid. Immediately after paracentesis, the venous pressure dropped to 8 cm. of saline. In the fluid there were no erythrocytes, the leukocytes could not be counted, and the differential count revealed 7 per cent neutrophils and 93 per cent lymphocytes. The total protein was 5.8 Gm. per 100 cc. Acid fast organisms were noted on direct smear of the fluid; however, guinea pig studies were negative at six weeks.

On June 16, 1952, the patient was started on 1 Gm. of dihydrostreptomycin and 12 Gm. of para-aminosalicylic acid daily. After five weeks the dosage of para-aminosalicylic acid was reduced to 6 Gm. daily because of nausea and vomiting, and the dihydrostreptomycin to 1 Gm. twice a week. After four months para-aminosalicylic acid was discontinued, and for the following four months he received streptomycin, 1 Gm. twice a week, and isonicotinic acid hydrazide. The patient remained ambulatory during the period of streptomycin therapy and was apparently asymptomatic.

He was seen again on Feb. 24, 1953, when he complained of slight cough and minimal temperature elevation. He was advised to re-enter the hospital but did not do so as the symptoms subsided in a short time.

He continued relatively asymptomatic until three weeks prior to admission to this hospital when he developed a constant, aching pain that began under the left scapula and radiated anteriorly into the chest. This was associated with a substernal feeling of fullness, exertional dyspnea, and a mild nonproductive cough. He lost 6 pounds of weight during the month prior to admission. A chest roentgenogram on Aug. 7, 1953 again revealed a large cardiac silhouette. Streptomycin and para-aminosalicylic acid therapy was restarted and he was advised to reenter a hospital.

The past history was entirely negative for tuberculosis, chest trauma or symptoms suggestive of hypothyroidism.

At the time of examination the patient was thin, well-developed, and did not appear ill. The temperature was 98.6 F., respirations 20, pulse rate of 72 per minute and blood pressure 110/70 mm. Hg. The skin was warm and moist. A few small posterior cervical lymph nodes were noted. The lung fields were clear. The heart was enlarged by percussion to the left anterior axillary line. The heart sounds were distant, and no murmurs were heard. There was no pulsus paradoxus. Except for slight tenderness in the mid-epigastrium, the remainder of the physical examination was essentially negative.

Laboratory studies were as follows: Urinalysis negative; erythrocytes 4,650,000; hemoglobin 14.3 Gm.; leukocytes 7,900 with 6 per cent stab forms, 54 per cent segmented neutrophilic granulocytes, 25 per cent lymphocytes, 2 per cent monocytes, 12 per cent eosinophils, 1 per cent basophils; and sedimentation rate 20 mm. in 1 hour. The serology was negative. The blood urea nitrogen was 36 mg. per 100 cc., serum cholesterol 154 mg. per 100 cc., and the basal metabolic rate was plus 8 per cent. Three gastric washings were negative for acid fast bacilli on culture. A tuberculin skin test was positive. The venous pressure was 15 cm. of saline and circulation time (arm to tongue) was 11 seconds. The initial electrocardiogram was within normal limits. The chest roentgenogram (fig. 1*A*) revealed clear lung fields but a marked increase in the size of the cardiac silhouette. Fluoroscopy showed minimal pulsations of all cardiac borders.

Pericardial aspiration on September 1 yielded 250 cc. of turbid, red-orange fluid which contained many erythrocytes, epithelial cells and cholesterol

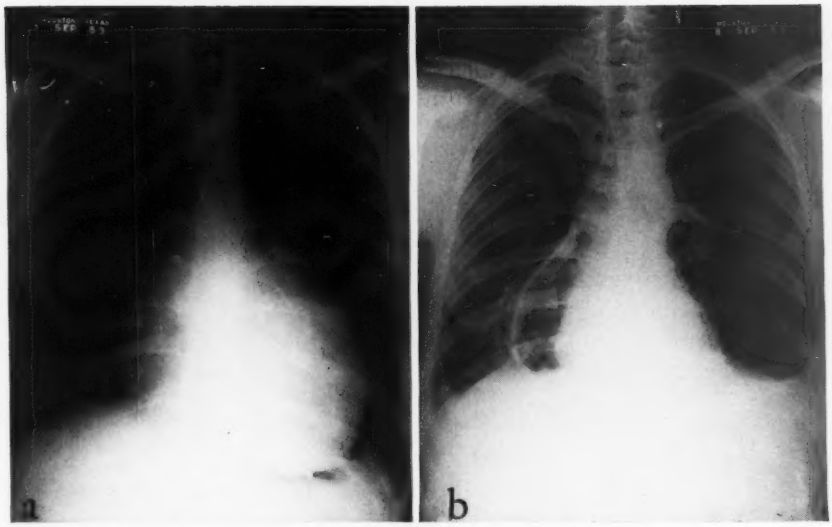

FIG. 1. *A*, chest roentgenogram on admission, showing increase in the size of the cardiac silhouette. *B*, roentgenogram taken after removal of 1700 cc. of fluid by pericardial aspiration and the injection of 850 cc. of air. The heart appears to be of normal size, but the pericardium is somewhat thickened.

crystals. The total protein was 8.5 Gm. per 100 cc. and the sugar was 19 mg. per 100 cc. Smear and culture of the fluid were negative for miscellaneous organisms as well as for acid fast bacilli. Several hours after the pericardial aspiration, the patient began to complain of substernal discomfort and epigastric pain which was accentuated by inspiration. The symptoms were progressive, and on Sept. 3 examination revealed distention of the neck veins, pulsus paradoxus, a pleural friction rub over the left lower anterior chest and clicking and bubbling sounds of air and fluid in the pericardial space. There was no pericardial friction rub. The venous pressure was 34.8 cm. of saline. Electrocardiogram revealed S-T segment elevation consistent with pericarditis. Pericardial aspiration yielded 1250 cc. of reddish iridescent fluid similar to that obtained previously. Examination of this fluid showed a specific gravity of 1.025, 1300 white blood cells per cubic millimeter, 450 erythrocytes per cubic millimeter, total protein 7.2 Gm. per 100 cc., sugar 12 mg. per 100 cc., and total cholesterol 263 mg. per 100 cc. (cholesterol content of supernatant fluid was 156 mg. per 100 cc.). Smears and cultures for miscellaneous organisms and acid fast bacilli, as well as guinea pig inoculations, were again negative.

Immediately following the pericardial aspiration, symptoms subsided somewhat, but over the next several days he again developed pain in the precordial region. Rales were noted in the left lung base and the liver became palpable 4 fingerbreadths below the right costal margin. On Sept. 7, 1700 cc. of brown-yellow fluid, which did not have the same iridescent appearance, were removed. Bacteriologic studies were again negative. At the time of aspiration, 850 cc. of air were injected into the pericardial space. A roentgenogram of the chest (fig. 1b) showed a large amount of air about a normal sized heart and the pericardium appeared thickened.

Over the following two weeks a pericardial friction rub and splashing sounds were noted intermittently. During the seven weeks following the last aspiration, the patient had an intermittent low grade fever. Because of the possibility of tuberculous pericarditis, streptomycin 1 Gm. daily, and isonicotinic acid hydrazide, 100 mg. three times a day, were started on Sept. 9 and two weeks later sodium para-aminosalicylic acid, 4.0 Gm. four times a day, was added. On Sept. 9, I^{131} uptake studies revealed a decreased iodine uptake (5.4 per cent in 3 hours, 5.3 per cent in 6 hours, 5.6 per cent in 24 hours) compatible with hypothyroidism. However, three repeat I^{131} uptake studies after para-aminosalicylic acid had been discontinued were normal, the one on Nov. 17 being 8.6 per cent in 3 hours, 10.0 per cent in 6 hours, 18.9 per cent in 24 hours, and 19 per cent in 48 hours. Repeat chest roentgenograms on November 13, (fig. 2), revealed marked diminution of the pericardial air, and the fluid level was again noted. On Dec. 1 the patient was transferred to the Surgical Service.

On Dec. 3 a left thoracotomy was performed through the fourth intercostal space anteriorly. The pericardium was gray-yellow and intimately adhered to the surface of the heart. The mediastinal pleura was incised and the phrenic nerve mobilized and retracted away from the pericardium. A longitudinal incision was made over the left lateral aspect

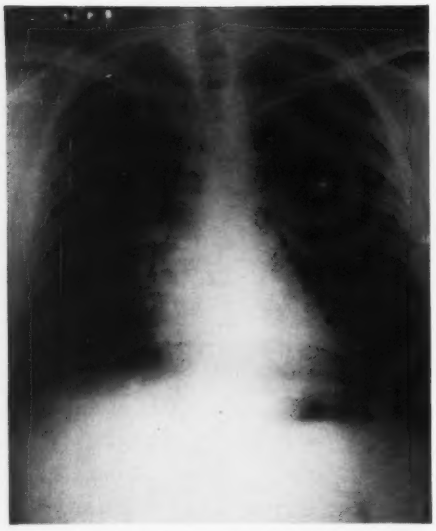

FIG. 2. Roentgenogram of the chest two months after admission, showing persistence of a pericardial fluid level.

of the pericardial sac and carried down to the myocardium. There was a layer of fibrous connective tissue intimately adherent to the epicardium and between this layer and the thickened pericardium there were numerous cyst-like spaces containing straw-colored fluid and numerous yellow plaques. The pericardium varied in thickness from 0.6 cm. over the ventricles to 0.2 cm. over the atria. Dissection of the pericardium was carried superiorly to the atrioventricular groove, laterally to include the surface of both right and left ventricles, and over the diaphragmatic surface of the heart. As the thickened, constricting pericardium was removed from the surface of the ventricles there was a noticeable increase in heart size. Upon completion of the pericardiectomy an intercostal catheter was inserted for underwater drainage of the chest and the thoracotomy wound was closed.

The patient's convalescence was uneventful and he was discharged on December 18, 1953.

Pathologic Findings: The specimen consisted of multiple portions of soft membranous tissue of varying thickness, the largest 10 by 8 cm. All surfaces were ragged with adhesions and here and there were bright yellow plaques up to 2 by 1.5 cm. The cut surfaces were firm, shiny white with some hemorrhagic areas.

Microscopic examination (fig. 3) revealed hyalinized connective tissue focally infiltrated with lymphocytes, plasma cells, and large mononuclear cells, with occasional aggregations of lymphocytes amounting to lymph follicles. In many areas foam cells were interspersed with lymphocytes and occasional giant cells of the foreign body type. There were a few slit-like spaces resembling cholesterol clefts. Sudan IV stains were positive for lipid in the

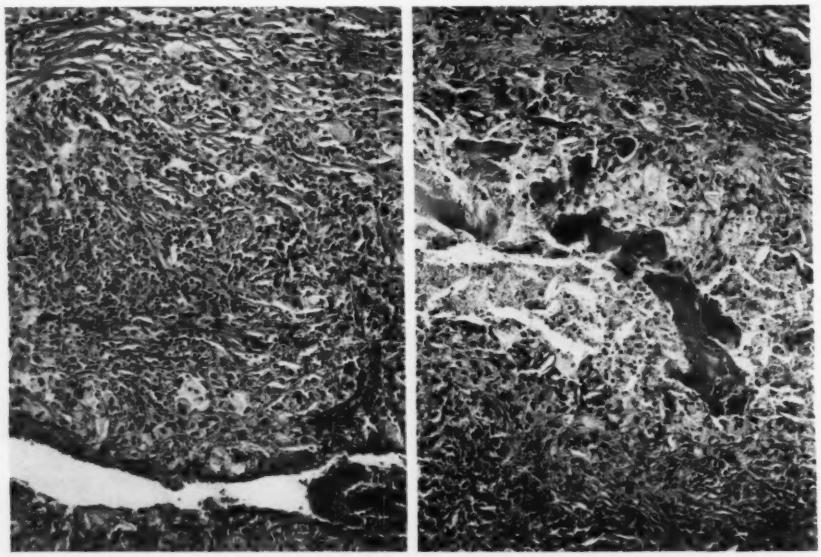

FIG. 3. Microscopic appearance of pericardium. In a dense hyalinized fibrous connective tissue are aggregates of slit-like spaces, few giant cells of the foreign body type, many foam cells and some lymphocytes and plasma cells. × 100.

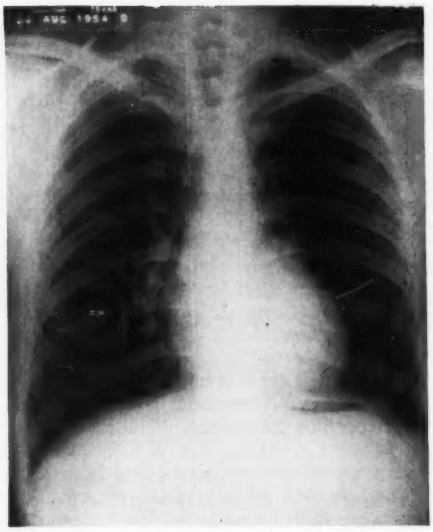

FIG. 4. Roentgenogram of the chest nine months after pericardiectomy, showing a normal cardiac silhouette.

foam cells. The substance contained in the cells was isotropic.

On Aug. 20, 1954, about nine months after operation, the patient was asymptomatic and chest roentgenogram revealed a normal cardiac silhouette (fig. 4).

COMMENT

The etiology of the constrictive cholesterol pericarditis is obscure in this case. Although acid fast organisms were noted on one direct smear of the pericardial fluid, subsequent studies failed to confirm this. Repeated cultures and guinea pig inoculations were negative, and there was little if any clinical response to long-term anti-microbial therapy during the first year of the patient's illness. Furthermore, histologic examination of the resected specimen failed to disclose any changes indicative of tuberculosis. While continued antibiotic therapy might have eradicated all evidence of tuberculosis, this seems inconsistent with the course of the disease.

There were no clinical manifestations suggestive of hypothyroidism, though there was an initial low I^{131} uptake. However, para-aminosalicylic acid was being administered at the time this test was performed thus invalidating the results.[11] Several subsequent I^{131} uptake studies after discontinuation of para-aminosalicylic acid were normal and no other laboratory studies were compatible with a diagnosis of hypothyroidism.

No history of chest trauma was obtained and neither the fluid removed by paracentesis nor the findings at operation suggested hemopericardium.

Recent observations by Ehrenhaft[12] indicate that lipids in high concentration within the pericardial sac may produce constrictive pericarditis. He injected autogenous whole blood into the pericardial sac of one group of dogs and in another the blood lipid fraction alone was injected. When sacrificed at intervals of one to six months later, in all of the animals there were changes in the pericardium and epicardium, but only those having intrapericardial injection of lipids had advanced constrictive pericarditis. These changes consisted of pericardial and epicardial thickening, areas of granulation tissue and adhesions. Fat stains revealed lipid material in cells within the thickened pericardium and epicardium.

In view of this experimental study, it is postulated that a high cholesterol content of the pericardial fluid was responsible for the constrictive pericarditis in this case. However, the factors responsible for the accumulation of cholesterol within the pericardial sac are not apparent.

SUMMARY

Pericardial effusion with a high cholesterol content is usually associated with myxedema. Tuberculosis and hemopericardium have also been considered of etiologic significance in cholesterol pericarditis.

The successful treatment of a case of chronic constrictive cholesterol pericarditis by pericardiectomy is reported. On the basis of experimental studies it appears that high concentrations of lipids in the pericardial fluid may produce pericarditis.

SYNOPSIS IN INTERLINGUA

Ben que pericarditis cholesterolic es usualmente associate con myxedema, illo pote occurrer in consequentia de infectiones tubercu-

lotic o de hemopericardio. Il pare que constriction cardiac es un tracto inusual del condition.

Un caso de chronic constrictive pericarditis cholesterolic esseva tractate per pericardiectomia con complete alleviamento del symptomas. Studios bacteriologic e histologic del resectionate pericardio non revelava le base etiologic del accumulation de cholesterol intra le sacco pericardial.

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Visualization of the Coronary Sinus in Cineangiocardiography

By Frank Campeti, M.D., Raymond Gramiak, M.D., James S. Watson, M.D., George H. Ramsey, M.D. and Sydney Weinberg

Reflux opacification of the coronary sinus was observed in 25 of 100 cases examined by cineangiocardiography. Of the 25 coronary sinus "positive" cases, 88 per cent were found to have cardiovascular lesions which are regularly associated with severe hypertension of the right heart chambers. The x-ray anatomy of the opacified sinus in different projections, and the movements by which it can be identified on x-ray motion picture films, are described in detail. The meaning of the reflux is discussed in relation to the diagnostic findings.

IN THE past decade the increasing accessibility of the living, human heart through catheterization and x-ray contrast technics has led to a renewal of interest in the coronary venous system, and to a repetition of older experiments under more physiological conditions. The human coronary sinus has been catheterized on numerous occasions, both accidentally and on purpose. Volume and pressure of flow have been measured and blood samples analyzed.[1, 2] Levine and Goodale[3] have taken advantage of the catheterization technique to make an electrographic study, while Tori[4] and others[5] have outlined the coronary venous system by retrograde injection of contrast material into the catheterized coronary sinus.

That the mechanism which guards the orifice of the coronary sinus breaks down under stress, permitting retrograde flow of right atrial blood into the coronary venous system, has long been suspected, and indeed was stated as a certainty in 1902 by Keith,[6] though at the time there was no way of observing the phenomenon in living, human subjects. However, in 1950, Gordon, Brahms and Sussman[7] reported contrast visualization of the coronary sinus (presumably by reflux) in two out of approximately 1200 routine angiocardiograms.

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A considerably higher incidence of coronary sinus opacification has been noted in a series of cineangiocardiograms made at motion picture frequencies in this department. The present paper describes the x-ray appearance of the coronary sinus reflux and offers a discussion of its meaning.

Material and Method of Study

Cineangiocardiograms of the 100 most recent cases examined in this department form the basis of the study. The clinical work-up of each patient includes physical examination and electrocardiogram. Successful cardiac catheterization studies were obtained in 31, while surgical findings have become available in 15 and autopsy findings in four.

The cineangiocardiograms of children were exposed on either 35 or 70 mm. film at camera speeds of 7½, 15, or 30 frames per second; those of adults on 35 mm. film at speeds of 7½ or 15 frames per second. Details of the procedure have been described elsewhere.[8, 9] Sixteen mm. reduction prints were made from the negatives and viewed on a special slow speed projector developed in this department.[10] Also, paper enlargements from the negatives were used for study and comparison of individual frames.

In the interest of better orientation, the following brief anatomical study was undertaken. Two normal hearts, obtained at autopsy, were injected with colored plastic material, following the method described by Tobin.[11] The left chambers and coronary arteries were injected with red plastic and the right chambers with blue. The coronary sinus and cardiac veins were injected with blue plastic to which 10 per cent iodoform had been added to give radiopacity. Each of the injected hearts was attached to a rotating table in approximately normal anatomical position (Morris, Testut). Full scale x-ray films were made of the hearts at 30 degree intervals through 360 degrees of rotation, as shown in figure 1. Also, conventional and stereo[12] x-ray motion pictures were

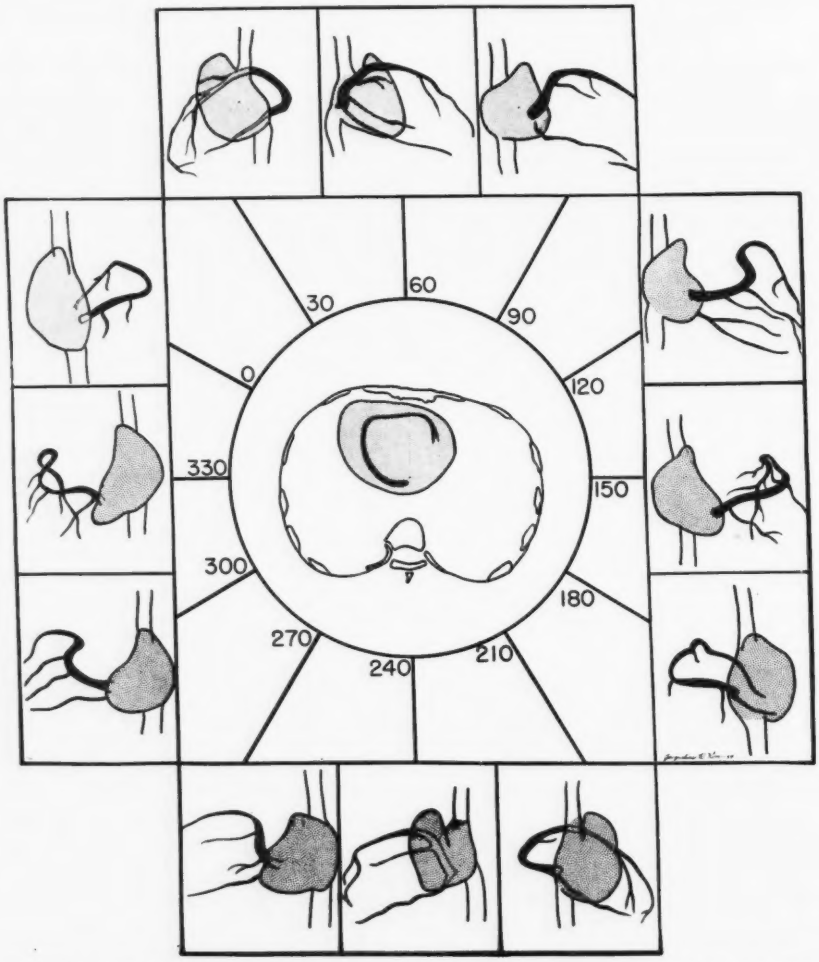

FIG. 1. Schematic drawing of normal coronary sinus and veins in 12 projections, made from radiographs of contrast injected hearts (see text). The figure at zero degrees represents the routine left anterior oblique view. Right atrium is shown distended by injection.

exposed as the hearts were moved clockwise through a complete revolution. The casts of the heart chambers and coronary vessels were then freed of surrounding tissue by digestion with hydrochloric acid, providing a three dimensional model which could be compared with the x-ray films and serve as an aid in identifying x-ray detail in different projections.

X-RAY ANATOMY

The x-ray appearance and relations of the coronary sinus vary considerably in different projections, as shown in figure 1. In the left anterior oblique view, the sinus is seen to arise from the septal border of the lower medial corner of the right atrium, variously termed "the *appendix auricularis* of His" or "the subeustachian sinus of Keith". From it the coronary sinus extends toward the left side of the heart and upward so as to form an angle of 40 to 70 degrees with a line drawn between the caval orifices.

Two unusually clear left anterior oblique views of the opacified coronary sinus are reproduced in figures 2 *A* and 3 *B*. However, the less conspicuous view in figure 4 *B* is more

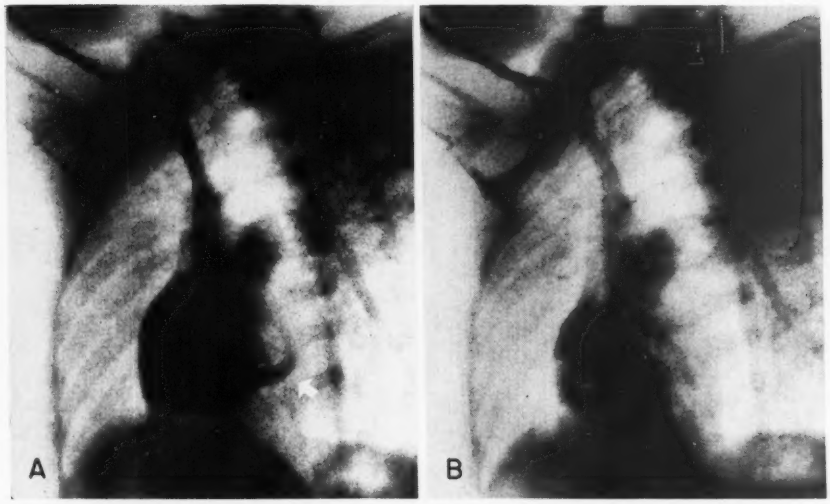

FIG. 2. Enlarged frames from a cineangiocardiogram during the stage of right heart filling. Patient is in left anterior oblique position. *A*. Arrow points to coronary sinus opacified by reflux of contrast material from right atrium. *B*. One fifth second later. The coronary sinus is no longer visible, but the inferior vena cava and hepatic vein are now densely opacified by reflux.

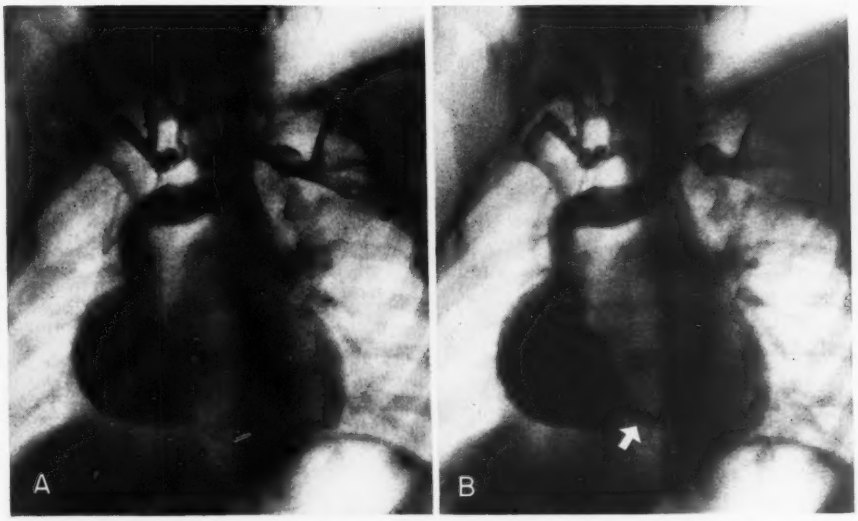

FIG. 3. Alteration in normal course of coronary sinus in a 6 year old patient with mitral disease. *A*. Opacified right atrium is in diastole. *B*. One fifteenth second later. Atrial systole is just beginning. Opacified coronary sinus is displaced downward by greatly enlarged left atrium. Opacification of pulmonary artery occurred two fifteenths second later.

typical of the general run of visualizations in our series. The frames reproduced are from the early stages of the angiocardiograms when opacification is pretty well confined to the systemic veins and right heart chambers. In later cardiac cycles the picture often becomes so complex that the recurring opacifications of the sinus and its tributaries can only be

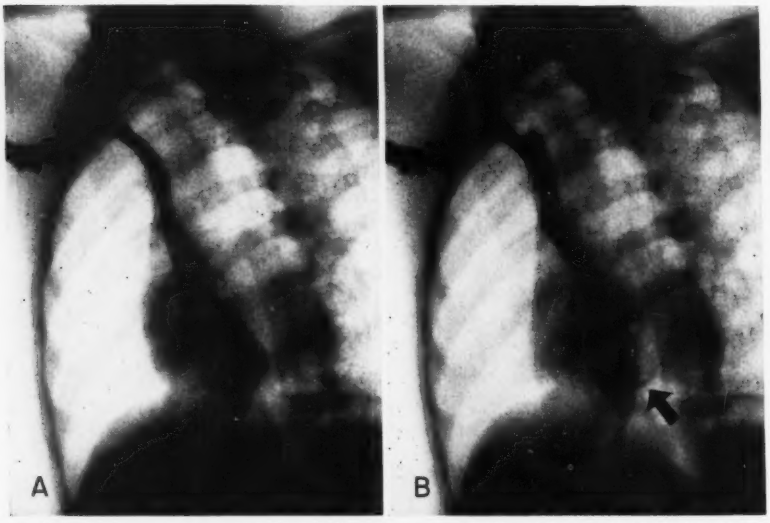

FIG. 4. Inconspicuous coronary sinus reflux in a 5 year old patient with Fallot's tetralogy. *A*. Wide lower end of superior vena cava indicates that atrium is in diastole. Coronary sinus is not visible. *B*. Two fifteenths second later. Atrium is now in systole. Coronary sinus is partially opacified (arrow). Inferior vena cava and hepatic vein are also opacified by reflux.

distinguished by a combination of still and motion viewing, or, at best, by a careful study of much longer sequences of frames than can be conveniently reproduced here.

The characteristic movements of the coronary sinus are closely related to those of the atrioventricular septum. In the left anterior oblique view, the sinus moves along a diagonal path, upward and to the right in atrial systole, and downward and to the left in atrial diastole. The sinus is easily distinguished from the lung vessels, since the principal excursions of the latter are respiratory. Their relatively small intrinsic and transmitted pulsations, although timed with the heart beat, are quite different in character from the wider movements of the coronary sinus.

In the right anterior oblique view both the subeustachian sinus and the coronary sinus tend to be hidden by the opacified right atrium. Quite often, however, contrast material penetrates as far as the great cardiac vein, which can be seen in the window between the atrium and the right ventricular outflow tract. Like the coronary sinus, the cardiac vein moves along a diagonal path and is thereby easily distinguished from the horizontally moving right auricular appendage.

Not all of the contrast visualizations of the coronary sinus were due primarily to reflux. In case 24 of table 1 the contrast injection reached the right atrium by way of a left superior vena cava, which emptied, as such veins usually do,[13] directly into the coronary sinus. When the film is projected, the stream of contrast material is seen to be compressed at the sinus orifice with each atrial systole, presumably by the partial closure of the coronary sinus valvular mechanism. It should be mentioned that a previous contrast injection via the right superior vena cava in this same patient resulted in the more usual reflux type of coronary sinus opacification.

INCIDENCE AND TIMING OF CORONARY SINUS OPACIFICATION

Twenty-five of the 100 cases of the series showed unmistakable opacification of the coronary sinus or its tributaries, in the unanimous opinion of five observers. The principal diagnostic findings of the 25 "positive" cases are given in table 1, where it will be noticed

TABLE 1.—*Cases Showing Opacification of the Coronary Sinus*

No.	Age	Principal Diagnostic Findings	Caval Reflux
1	1 yr.	Tetral. of Fallot	+
2	2	Pulm. sten. I-A sept. def.	−
3	5	Tricusp. atres. I-A sept. def.	−
4	4	Tricusp. atres. I-A sept. def.	+
5	3 mo.	Tricusp. atres. I-A sept. def.	+
6	12 yr.	Pulm. hypertens. Revised pat. duct.	+
7	15	Tetral. of Fallot	−
8	4	Pulm. sten. I-A sept. def.	+
9	6	Pulm. sten. Pat. duct.	+
10	12	Pat. duct.	−
11	6	Pulm. hypertens. Revised pat. duct.	+
12	5	Pulm. sten. I-A sept. def.	−
13	5	Pat. duct.	+
14	4	Pulm. sten. (?)	+
15	6	I-A sept. def. Mitral sten. Coarct.	+
16	8	Pulm. sten.	+
17	15	Pulm. sten.	−
18	2	Pulm. sten. I-A sept. def.	+
19	5	Pulm. sten. I-A sept. def.	+
20	9	Pulm. sten.	+
21	10	Pulm. hypertens. I-V sept. def.	+
22	12	Pulm. sten.	+
23	6 mo.	I-A sept. def.	−
24	6 yr.	Pulm. sten. Left sup. vena cava	−
25	5	Tetral. of Fallot	−

that the majority (88 per cent) had cardiovascular anomalies which are known to be regularly associated with severe right heart hypertension. Counted as exceptions were two cases of uncomplicated patent ductus and one case in which the tentative diagnosis of pulmonary stenosis is still in doubt. Twelve of the 25 were successfully catheterized, and in all but one (a case of patent ductus), severe hypertension of one or both of the right heart chambers was recorded.

Of the 75 coronary sinus "negative" cases, on the other hand, only 24 (32 per cent) had lesions which would be expected to produce severe right heart hypertension. Nineteen of the 75 were successfully catheterized, and hypertension was found in nine. It is quite possible, of course, that, in some of the cases which we have listed as negative, the coronary sinus reflux was actually present but was missed because of unfavorable positioning.

As to the timing of the reflux in the heart cycle: it was observed to occur in successive atrial systoles, that is, at the times when intra-atrial pressure is high and pressure within the sinus, low. Rarely, opacification of the sinus persisted into atrial diastole. Column 4 of table 1 indicates the cases showing reflux not only into the coronary sinus but also into the inferior vena cava. The two refluxes seldom began at the same instant, the caval reflux appearing sometimes in atrial systole and sometimes in diastole.

DISCUSSION

Before attempting to draw conclusions from our data, we are first obliged to ask: (1) Is the coronary sinus reflux physiological? (2) Is the coronary sinus reflux an artefact of the angiocardiographic technic? In order to answer the first of these questions it would be helpful to be able to refer to a long series of cine-angiocardiograms of normal persons. Unfortunately, all that we have in this line is a series of examinations of 18 patients with apparently normal circulatory systems but with tumors of the lung or mediastinum. The fact that none of these examinations showed the coronary sinus reflux, although suggestive, is hardly conclusive.

Nor is anything very definite on this subject to be found in the literature. Johnson and Wiggers[14] reproduced curves "showing the velocity changes in sinus flow when the blood is led back into the superior vena cava," and they pointed out the presence of occasional negative waves, presystolic in time. However, they were unable to convince themselves that such waves represented "actual backflow" and attributed them instead to movements of the catheter tip. From this we gather that Johnson and Wiggers would have voted "no" in answer to our first question, but not categorically. Indeed, it is hard to see how experiments which depend on the presence of a catheter in the coronary sinus orifice and which by-pass the right atrium could give a final answer in a

problem involving the free action of these structures.

The second question is one which has often been raised before in regard to right-to-left interatrial and interventricular shunts, caval refluxes, and other angiocardiographic phenomena. Dotter and Steinberg[15] concluded from catheterization studies that rapid contrast injections might sometimes cause a right atrial pressure rise in infants and young children. However, even if the increase in pressure were sufficient to reverse the rather small pressure gradient[3] between sinus and atrium, it would not necessarily be expected to overcome the mechanism which guards the coronary sinus orifice; especially if we accept Keith's view that the orifice is closed during atrial systole, not by the inconstant thebesian valve, but by contracting right atrial muscle groups.

In this connection the distinction made by Hedman, Lind, and Wegelius[16] between systolic and diastolic *caval* refluxes may be of interest. They argue that caval refluxes occurring in atrial diastole (when both caval orifices are open) are probably accidental, whereas those occurring in atrial systole (when, according to "fast" angiocardiographic observations, both orifices are normally closed) must be regarded as having diagnostic significance. But if we attempt to extend this distinction to the coronary sinus reflux, we run into ambiguities. For how can we reconcile a systolic coronary sinus reflux and a diastolic caval reflux occurring in the same case?

As a matter of fact, the analogy between the caval and the coronary sinus reflux is by no means perfect. Thus, while intracaval pressure, which opposes the caval reflux, is generally higher in atrial systole, the analogous pressure within the coronary venous system regularly reaches its peak in atrial diastole. Furthermore, intracaval pressure is much more influenced by random respiratory movements than is pressure within the coronary veins. These differences probably explain why the caval refluxes referred to in table 1 were observed more often in atrial diastole than the coronary sinus refluxes.

Our own impression of the meaning of the coronary sinus reflux is naturally influenced by the diagnostic correlations of our particular series of cases. These lead us to think that the majority of refluxes observed are of diagnostic significance. By way of testing this impression we have made it a working rule that, whenever the reflux is seen, right atrial and right ventricular hypertension should be suspected and looked for. In most cases, of course, the diagnosis will be indicated by other angiocardiographic signs, but in pulmonary stenosis, where the angiocardiogram is often deceptively "normal," the coronary sinus reflux may turn out to have practical value.

Before ending the discussion, we should like to return briefly to Keith's illuminating theory of right atrial dynamics already referred to. Keith maintained that the caval and coronary sinus orifices are normally closed during atrial systole by the contraction of certain right atrial muscle groups which he demonstrated by special dissections. These "valvular mechanisms", as he called them, are unmentioned in the textbooks, probably because they were not susceptible of investigation by prevalent catheterization methods. Recently, however, Keith's views have received support from "fast" (10 exposures per second) angiocardiographic studies of the caval orifices by Hedman, Lind, and Wegelius, and from our own cinefluorographic observations of the behavior of the coronary sinus orifice during a contrast injection which reached the right atrium through the coronary sinus (table 1, case 24).

Concerning the coronary sinus valvular mechanism, Keith stated with characteristic assurance that it would be "the next to fail after that of the inferior vena cava;" though actually our figures for the two types of reflux (table 1, column 4) suggest that the reverse of Keith's pronouncement may be true, at least in congenitally abnormal hearts which are not in failure. Keith further implied that the valvular mechanism breaks down in cases of "venous back pressure" because of weakening and dilatation of the right atrial wall; a concept which is corroborated to some extent by Condorelli's[17] study of the degeneration of the atrial venous system in chronic valvular disease and by Hellerstein and Orbison's[18] observa-

tion that the coronary sinus orifice is consistently enlarged in the diffusely dilated hearts of clinical congestive heart failure. On this basis we should expect to find, and so far generally have found, in cases of congenital heart disease showing the coronary sinus reflux, not necessarily congestive heart failure, but persistent right atrial hypertension and enlargement. The fact that the majority of these cases have right ventricular hypertension also, is explained when it is remembered that hypertension in the ventricle is one of the commonest precursors of hypertension in the atrium.

Summary

Reflux opacification of the coronary sinus and/or its tributaries was noted during contrast filling of the right heart in 25 of a series of 100 cineangiocardiographic examinations. The reflux appeared in atrial systole and disappeared, as a rule, in diastole. It was frequently accompanied by reflux into the inferior vena cava, the latter appearing more often in atrial diastole.

Caval opacification is easy to detect, but the opacified coronary sinus tends to be confused with other opacified vessels, and is sometimes only identifiable by its characteristic movements. These are described, and the x-ray appearance of the sinus in different projections is shown in diagrams.

Of the 25 coronary "positive" cases in the series, 88 per cent had cardiovascular anomalies which are regularly associated with severe right heart chamber hypertension. Of the 75 "negative" cases, only 32 per cent had such lesions. While these figures do not establish a one-to-one correspondence between the reflux and hypertension, they suggest that something more than a temporary reversal of the pressure gradient is needed to assure a retrograde flow into the coronary veins. This "something more" is believed to be the breakdown of the coronary sinus valvular mechanism.

Keith's theory that the caval and coronary sinus orifices are normally closed during atrial systole by the combined action of certain right atrial muscle groups, though insusceptible of proof by catheterization methods, has recently received support from "fast" angiocardiographic and cinefluorographic observations. Given a coronary sinus valvular mechanism of this sort, its breakdown in cases of severe right heart chamber hypertension can be explained on the basis of the associated impairment of function of the right atrial myocardium.

Acknowledgment

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Summario in Interlingua

Opacification per refluxo esseva observate in le sinus coronari e/o su tributarios post infusion de substantia a contrasto in 25 casos de un serie de 100 examines cineangiocardiographic. Le refluxo appareva in systole atrial e dispareva generalmente in diastole. Frequentemente illo esseva accompaniate de refluxo a in le vena cava inferior, sed isto appareva plus frequentemente in diastole atrial.

Le configuration roentgenographic del sinus in varie projectiones es monstrate diagrammaticamente.

Le 25 casos "positive" (i.e. a refluxo coronari) includeva 88 pro cento de patientes con anomalias vascular del typos regularmente associate con sever hypertension del camera dextere del corde. Le 75 casos "negative" includeva solmente 32 pro cento de patientes con tal lesiones.

Iste datos pare indicar que le conditiones necessari pro effectuar un fluxo retrograde a in le venas coronari include plus que un reversion temporari del gradiente pressional. Nos opina que iste "plus" es le dysfunctionamento del mechanismo valvular del sinus coronari.

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Association of Hypotensive State in Myocardial Infarction with Subsequent Metabolic Reponses and Mortality in Elderly Subjects

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With the assistance of Thomas B. Smart, M.D., Robert Neilsen, M.D. and
Emily R. Carlson, B.S.

Ten elderly patients with typical findings of acute myocardial infarction were studied for two weeks on a metabolic ward. Blood pressures were determined hourly, and balances of nitrogen, water and electrolytes were computed daily. Surviving patients had higher blood pressures, lower heart rates, lost more weight, exhibited negative sodium balance and had earlier recovery from negative nitrogen and potassium balance. Early appearance of hypotension presaged clinical complications, unfavorable metabolic responses and a fatal outcome.

HYPOTENSION occurring in patients with myocardial infarction is associated with increased mortality when shock is present.[1-5] Many of these patients in shock succumb despite treatment with pressor amines.[6-11] Such patients undergo severe stress and the high mortality raises the question of the adequacy of the metabolic responses.

Only a few studies describing the metabolic responses to myocardial infarction have come to our attention despite the plethora of communications dealing with the entity. Wilhelm reported in 1951 increased concentrations of serum potassium in all of 10 patients following myocardial infarction.[12] Serum sodium concentrations were below 133 m.Eq. per liter in seven patients. Donzelot and Kaufman noted eosinopenia and increased urinary excretion of 11-oxysteroids and 17-ketosteroids in four patients between the third and fifth days after infarction, and depressed excretion from the seventh to the fourteenth day.[13] Such changes were interpreted as evidence of adrenal cortical reaction to injury.

The metabolic response to myocardial infarction would seem to be of particular importance in the elderly subject because of the associated high mortality. A recent survey by Smart of 160 patients admitted to the King County Hospital (Seattle) with a diagnosis of myocardial infarction and covering a 30-month period indicated an overall mortality of 74 per cent, one-third dying within the first 24 hours.[14] Besides advanced age (males averaged 67.4 years, females 70.4 years), most of these patients had clinical pathologic findings associated with a poor prognosis. The mortality was 96 per cent in 26 patients in shock, despite treatment with norepinephrine, while it was only 80 per cent in 36 untreated patients also in shock. Although the study conducted by Smart was not a controlled one, but a survey of the clinical records, it raises the question of the importance of hypotension after myocardial infarction in the elderly subject.

This report differentiates the hypotensive and metabolic responses in elderly patients who died from myocardial infarction from the changes occurring in those patients who survive. For the purposes of this study, hypotension was defined as systolic pressure below 90 mm. Hg.

Material and Procedure

Preliminary Observations

From August to December 1953, serum and urinary electrolytes were studied for seven-day periods in 15 consecutive patients with acute myocardial

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These studies have been supported in the past by Grant-in-Aid from the Washington State Heart Association.

Dr. Bergy is a Trainee of the National Heart Institute, 1954–1955.

TABLE 1.—*Preliminary Survey of Electrolyte Changes with Acute Myocardial Infarction (Mean Values in 15 Patients)*

	Post-Infarction days						
	1	2	3	4	5	6	7
Serum Concentration							
K, mEq/L.....	4.7	5.0	5.0	5.0	5.1	5.1	5.2
Na, mEq/L....	142	143	140	142	141	142	140
Urinary Excretion							
24 hr. volume, ml.....	909	840	924	1233	1211	1104	1135
24 hr. Na, mEq.	67	40	40	47	32	31	25

infarction (table 1). There was very slight elevation of serum potassium concentration from an initial value of 4.7 to 5.2 mEq per liter, and possibly slight renal conservation of sodium during this period. Since these patients were on the general wards of the hospital, it was not feasible to determine accurately the dietary intakes. These observations suggested that metabolic responses occurred after infarction, but the paucity of information precluded an adequate description.

Clinical Material

Seven men and three women, ranging in age from 52 to 82 with a mean of 72.2 years, were admitted to the Metabolic Ward with typical findings (table 2). Clinical shock was manifest on admission in one patient; four other patients exhibited hypotension. Based upon Schnur's Pathologic Index Ratings[5] after the first day, the predicted mortality ranged from 50 to 75 per cent.

Methods

Each patient was attended by a special nurse for 24 hours daily for two weeks. Blood pressures and heart rates were obtained hourly around the clock. Fluid intake and output were recorded, and daily body weights were obtained (Invalift). A trained dietitian estimated intake of calories, nitrogen, potassium, sodium and chloride daily[15]. Sodium intake was limited to 400 mg. (17 mEq.), whereas calories were permitted *ad libitum*.

Vital capacity, venous pressure (with zero reference level 10 cm. above mattress with patient supine), arm-to-tongue circulation time (Decholin), erythrocyte sedimentation rate and hematocrit were done regularly two to three times weekly. Daily sodium and potassium concentrations in serum and urine were determined using a Baird flame photometer, with an internal lithium standard[16]. Nitrogen was determined by a modified urease method[17]. "Crude water balance" was calculated from the difference in measured intake and measured urine excretion, disregarding insensible, sweat and fecal losses, but including any emesis. Marked diaphoresis was observed in only one subject, W. G., who had shock on admission and survived. None had any diarrhea. "Crude balances" for nitrogen, sodium and potassium were determined in a similar manner. The volume-distributions of Evans blue[18] and sodium thiosulfate[19] were determined during both the first and second weeks in six of the patients.

Three patients were treated with pressor amines for clinical shock (table 3). Once blood pressure appeared to be stable clinically, and patients were free of symptoms or signs of shock, pressor amines were

TABLE 2.—*Clinical Findings on Admission in 10 Patients With Acute Myocardial Infarction*

Patient	Age, sex	History of:				Cyanosis	BP, mm. Hg	Clinical shock	Congestive failure	ECG, diagnosis of infarction	PIR* (Schnur)
		Angina pectoris	Previous infarction	Congestive failure	Hypertension						
Living:											
H. D.	79M	3 years	−	−	−	+	98/65	−	−	Anterior	20
W. G.	52M	6 years	+	+	?	++	90/50	++	++	Antero septal	125
M. B.	72F	1 year	−	+	+	−	220/126	−	++	LBBB	70
T. L.	71M	—	−	−	−	++	110/68	−	−	Posterior	20
Dying:											
N. McG.	77F	8 years	?	+	−	+	130/80	−	+	Anterior	60
C. K.	82F	5 mo.	−	−	+	++	70/50	−	+	Posterior	110
B. L.	71M	3 years	+	−	+	+	160/100	−	++	Anterior	65
D. v. T.	68M	1 year	+	−	−	+	98/72	−	+	Postero septal	70
A. B.	70M	1 year	−	−	−	++	102/68	−	++	Posterior	65
F. S.	80M	5 years	−+	+	+	++	134/80	−	++	Posterior	65
Mean.....	72.2	27 mo.					121/76				67

* Pathologic index rating.

TABLE 3.—*Clinical Course*

Patient	Cardiovascular complications				Treatment		Other complications	Outcome
	Shock	Arrhythmia	Congestive heart failure	Embolism	Pressor amines	Anticoagulant		
Living:								
H. D.	+	−	+	−	+	+		Recovered
W. G.	++	+	+	−	+	−		Recovered
M. B.	−	−	−	−	−	−	Cerebrovascular accident	Recovered
T. L.	−	−	+	−	+	−		Recovered
Dying:								
N. McG.	++	+	+	−	+	+	Cerebrovascular accident, pneumonia	Died suddenly 6th day
C. K.	++	+	+	?	−	−	Urinary tract infection	Died 14th day
B. L.	++	+	+	Pulm., R.L.L.	−	−		Died 28th day
D. v. T.	±	−	+	−	−	−	Urinary tract infection	Died 4th day
A. B.	−	−	+	−	−	−	Bronchopneumonia, cholecystitis	Died 21st day
F. S.	−	−	+	−	−	−	Urinary tract infection, bronchopneumonia	Died 27th day

discontinued despite the persistence of asymptomatic hypotension. All patients not already digitalized received digitoxin, because of appearance of congestive heart failure during their hospital course.

All observations were referred to the day of onset of myocardial infarction as determined from the clinical history. Following intensive study for two weeks, surviving patients were transferred to the general medical wards for further clinical observation. Death within four weeks after onset was attributed to myocardial infarction, even if other causes developed terminally. For study purposes, the data obtained on living patients has been grouped together for comparison with similar observations on patients who died within this four-week interval.

OBSERVATIONS

The clinical course was typical of patients with acute myocardial infarction observed in this hospital (table 3). Except for slightly higher temperatures (1 F.) in dying patients on the first two days, there was no difference in mean febrile responses between these two groups. The mean white blood cell count fell from 12,010 to 9,900 in the surviving patients, and it increased from 10,700 to 12,400 in the dying patients. There were negligible changes in sedimentation rate between these two groups. Severe clinical shock was present on admission in W. G. who survived, whereas it developed after admission in three other patients who subsequently died. One of these resulted in sudden death on the sixth day. A cerebrovascular accident occurred in two patients, but only C. K. who also developed pneumonia and an urinary tract infection died. Two other patients had their postinfarction course complicated by multiple infections which caused death on the twenty-first and twenty-seventh days. Congestive heart failure was present during the hospital course in all patients but M. B. This hypertensive patient had a history of angina pectoris and congestive failure for a year before; she had more failure and left bundle branch block (which obscured electrocardiographic evidence of infarction) on admission. Her physical findings and course were typical of myocardial infarction, nevertheless.

Six of the 10 patients died within 4 to 28 days from the onset of infarction. The primary cause of death in these patients was considered to be myocardial infarction, even though various contributory causes were present.

RESULTS

1. *Blood Pressure and Heart Rate*

Low blood pressure was a persistent feature in fatal cases (fig. 1). From the second to eighth days, the mean hourly systolic pressure

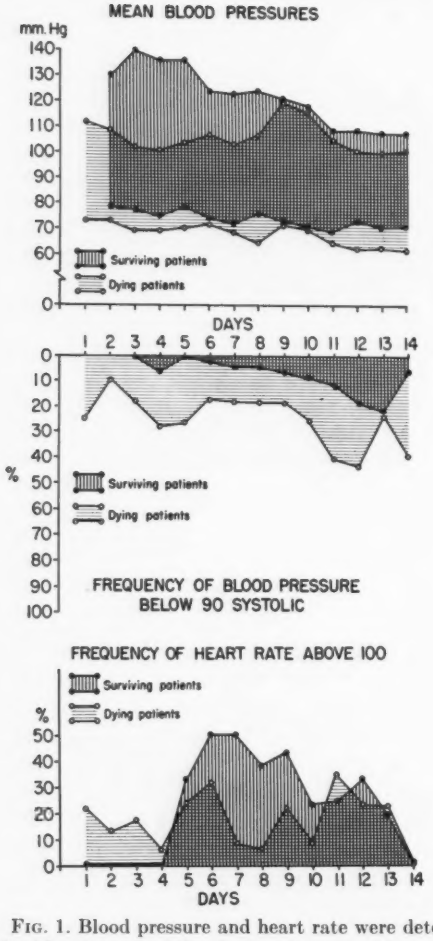

FIG. 1. Blood pressure and heart rate were determined hourly around the clock and averaged for each day. In the top figure, mean daily systolic and diastolic values are shown for the surviving and dying groups of patients. Frequencies of hypotension and tachycardia for the same groups are shown in two lower figures.

was 130 ± 7.6 mm. Hg (mean ± standard deviation) for the survivors versus 105 ± 3.1 for the dying patients ($p < .001$). Surviving patients had no hypotension (systolic pressure under 90 mm. Hg) during first three days. The mean systolic pressure of survivors gradually declined, until there was no significant difference in systolic pressure between surviving and dying patients after the first week. The hourly incidence of hypotension during the two weeks of observation was 24.9 ± 9.5 per cent for the dying patients versus 6.1 ± 6.4 per cent for the surviving patients ($p < .001$).

The hourly incidence of low diastolic pressures (under 60 mm. Hg) was 28.4 ± 5.1 per cent in surviving patients for the two-week period of study ($p < .001$). This difference was particularly marked during the second week.

The heart rate never exceeded 100 beats per minute for the first four days in the survivors (fig. 1), but it was frequently above 100 from the fifth to tenth days.

2. *Serum Cations*

The mean concentration of serum potassium ranged from 4.5 to 5.6 mEq per liter in surviving and dying patients (fig. 2). The mean concentration of serum sodium gradually fell in dying patients from an initial value of 143 to 134 mEq per liter in the second week (fig. 2).

3. *Metabolic Balances*

After the first five days, there was a slight, but significant difference ($p < .001$) in the daily sodium balance between surviving and dying patients (fig. 3). Due to the renal conservation of sodium in only the dying patients

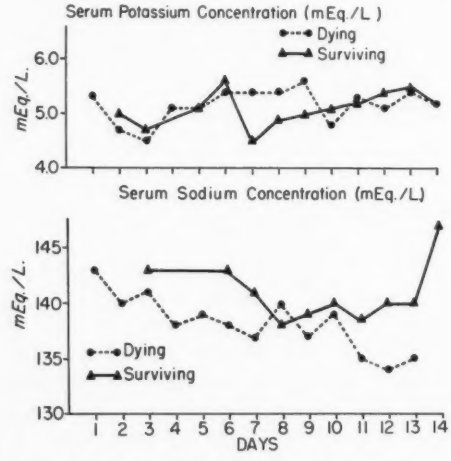

FIG. 2. Fluctuations in mean daily serum concentrations of sodium and potassium for patients who lived and those who died during the course of study.

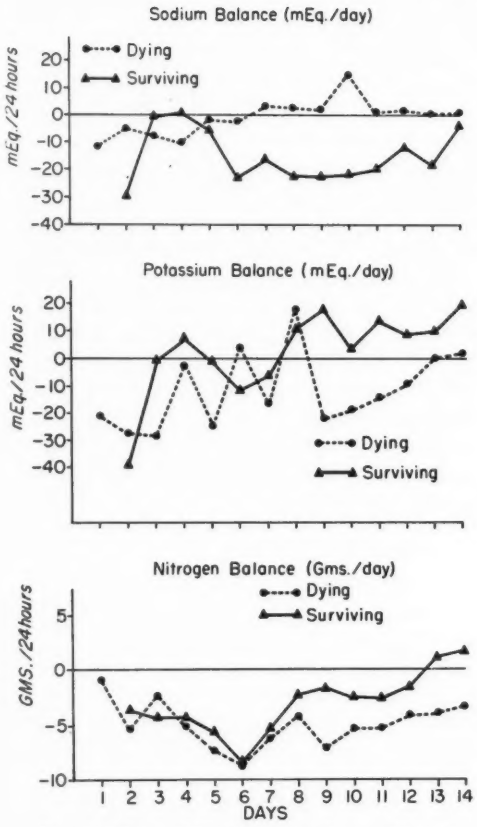

FIG. 3. Mean daily balances show sodium loss, along with more rapid return to positive potassium, and nitrogen balance in patients who survived.

from the sixth to thirteenth days, there was a mean cumulative difference of −137 mEq. sodium between these two groups.

Both nitrogen and potassium balances were negative initially in both groups of patients (fig. 3). The survivors recovered earlier, possibly due to greater caloric intake in these patients (fig. 4).

There was no significant difference in the crude water balances between these two groups (fig. 4). Despite this similarity and a greater caloric intake, but no significant differences in mean temperatures, the surviving patients still lost weight more rapidly (fig. 4). This latter difference suggested a better circulatory status and greater metabolic activity in surviving patients.

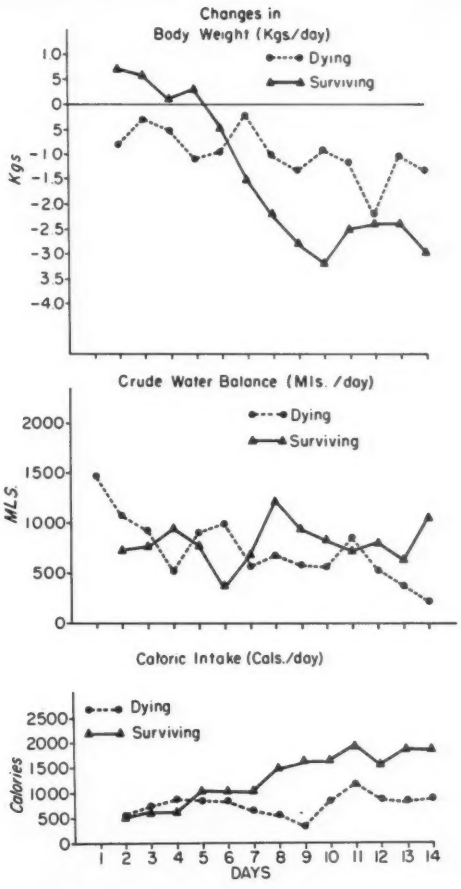

FIG. 4. Body weight decreased more rapidly in the surviving group, despite a higher caloric intake. There was no significant difference in crude water balances.

4. *Volume Distribution of Sodium Thiosulfate*

The changes in mean body weight and volume-distributions of sodium thiosulfate and Evans blue (T-1824) are shown in figure 5. There was a 4.5 per cent reduction in weight and 12 per cent decrease in volume-distribution of sodium thiosulfate from the first to second weeks in surviving patients. Dying patients, in contrast, showed less change in weight and 12 per cent increase in the thiosulfate space. In all instances the mean thiosulfate spaces ranged from 15 to 18 per cent of the body weight.

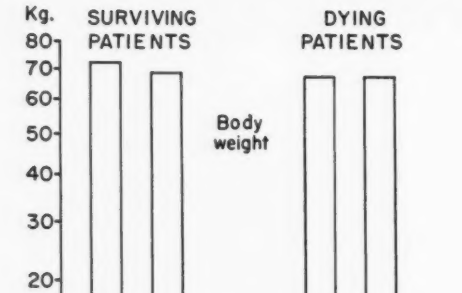

FIG. 5. Whereas patients who survived exhibited reductions in body weight and thiosulfate space during first two weeks, there was no corresponding change in body weight in patients who died.

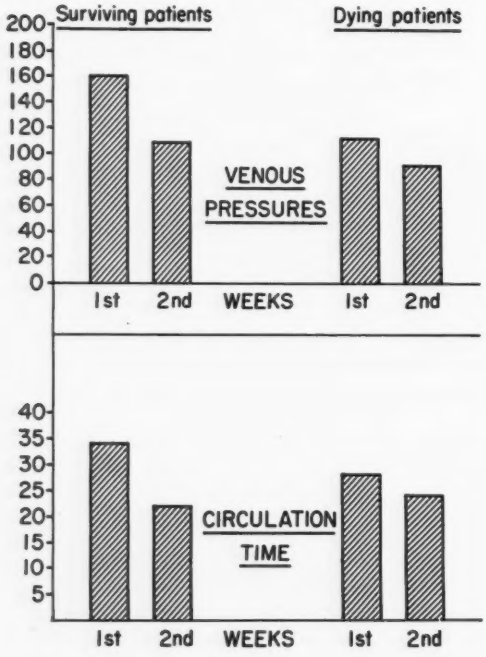

FIG. 6. Both the average venous pressure and circulation time diminished from first to second weeks in surviving and dying patients.

5. *Derived Blood Volume*

There was a negligible decrease in Evans blue space and derived red blood cell volumes (fig. 5), together with a slight rise in hematocrit from 38.3 to 40.3 per cent in surviving patients. The hematocrit fell in the dying patients from 41.8 to 36.3 per cent.

6. *Venous Pressure and Circulation Time*

The mean values for venous pressure and circulation time in the two groups of patients during the first and second week are shown in figure 6. Not only did the surviving patients have a larger volume distribution of sodium thiosulfate initially and greater fall by the second week, but they also exhibited higher venous pressures and circulation times initially than the dying patients.

DISCUSSION

The average age, relative severity of pathologic findings and mortality of the 10 elderly patients described in this report were roughly comparable with that of 160 patients with the same diagnosis who were observed in King County Hospital.[14] Nevertheless, some selection was unavoidable, inasmuch as the patients had to survive the immediate vascular insult in order to be admitted to the Metabolic Ward for study. The 10 patients were representative of patients admitted to King County Hospital with myocardial infarction and surviving the first day. Due to the small number of patients studied, these observations only can be considered as preliminary.

Distinct differences were found in hypotensive, clinical and metabolic responses between patients who survived and those patients who died.

Although only two of the four surviving patients had congestive failure on admission in contrast to all six of the dying patients (table 2), venous pressure and circulation time were higher in the survivors initially. Thiosulfate space was also larger in these individuals.

Hourly observations of blood pressure continuously for two weeks revealed hypotension to be a conspicuous characteristic of patients who subsequently died. Not only was the

systolic pressure more frequently below 90 mm. Hg, but the diastolic pressure also was more commonly below 60 mm. Hg. There were phasic differences in incidence of heart rates over 100 per minute in addition.

Dying patients experienced more clinical complications than living patients (table 3). They ate less, lost weight more gradually, exhibited renal conservation of sodium, and more prolonged negative nitrogen and potassium balances. Thiosulfate space, venous pressure and circulation time were not as high initially, but thiosulfate space increased, rather than decreased, during the second week. Serum sodium concentration decreased slightly. These responses were compatible with adrenal cortical reaction to stress, but whether the magnitude of changes was proportional to myocardial and other insults remains unanswered. The fact that death occurred suggests the possibility of an inadequate adrenal cortical reaction, and raises the question of need for adrenal cortical supplementation. Lacking any data or quantitative differences in eosinopenia or urinary excretion of 11-oxy and 17-ketosteroids affords no opportunity for appraising this possibility. Furthermore, it is impossible to predict from these data whether hormonal therapy would be beneficial, as has been recommended by Breu.[20]

The fact that hypotension initially was one of the outstanding characteristics of dying patients indicates that observed clinical complications and quantitative differences in metabolic responses may well be associated with a hypodynamic circulation. Furthermore, the differences in venous pressure, circulation time and thiosulfate space suggest impaired mechanisms for venous return. An adequate evaluation of these possibilities awaits a study of serial hemodynamic observations in both living and dying patients.

Probably the major factor determining the prolonged circulation time was the central blood volume. Possibly surviving patients had more effective mechanisms for venous return of blood to the heart by virtue of the greater volume and pressure.

Finally, any inferences from this study to the overall problems of morbidity and mortality from myocardial infarction should be made with great caution due to the advanced age and small number of patients studied.

Summary

1. Ten patients with typical findings of acute myocardial infarction were studied for two weeks after admission to the Metabolic Ward of King County Hospital.

2. Six of these patients died of myocardial infarction and terminal complications within four weeks.

3. None of the survivors had hypotension or tachycardia, evaluated by hourly determinations, during first three days.

4. Systolic and pulse pressures diminished gradually in the survivors.

5. Surviving patients had higher mean venous pressures, circulation times and volume distribution of sodium thiosulfate initially, together with reductions in each of these factors during the second week. These changes were associated with greater loss of weight, negative sodium balance, and earlier recovery from negative potassium and nitrogen balances observed in these patients.

6. Dying patients exhibited a slight decrease in serum sodium concentration, renal conservation of sodium, expansion of volume distribution of sodium thiosulfate, as well as persistently lower blood pressures.

7. It is concluded that the early appearance of hypotension following acute myocardial infarction presaged clinical complications and unfavorable metabolic responses as well as a fatal outcome in these patients.

Summario in Interlingua

1. Esseva studiate 10 patientes con typic constatationes de acute infarcimento myocardiac. Le studios esseva executate al Sala Metabolic del Hospital de King County a Seattle. Illos coperiva 2 septimanas post le admission del patientes.

2. Intra 4 septimanas, 6 del patientes moriva de infarcimento myocardiac con complicationes terminal.

3. Nulle del superviventes habeva hypoten-

sion o tachycardia secundo le evalutation de determinationes executate a intervallos de un hora durante le prime 3 dies.

4. Le superviventes monstrava un reduction gradual del pressiones systolic e pulsar.

5. Le superviventes habeva initialmente plus alte valores median del pression venose, del tempore circulatori, e del distribution voluminic de thiosulfato de natrium. Omne iste factores monstrava valores decrescente in le curso del secunde septimana. Iste cambiamentos esseva associate con un plus grande perdita de peso, un negative balancia de natrium, e un plus prompte rectification de negative balancias de kalium e nitrogeno.

6. Le patientes qui moriva exhibiva un leve reduction del concentration de natrium seral, retention renal de natrium, expansion del distribution voluminic de thiosulfato de natrium, e un persistente e plus marcate hypotension.

7. Nos conclude que le precoce apparition de hypotension post acute infarcimento myocardiac esseva in iste patientes un presagio de complicationes clinic e de disfavorabile responses metabolic a termino mortal.

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Circulatory Dynamics in Osteitis Deformans

By J. LEQUIME, M.D. AND H. DENOLIN, M.D.

In Paget's disease the peripheral blood flow is increased in the bones affected by the disease. Nevertheless the circulatory dynamics of the patients studied *at rest* are usually not modified significantly. But during *exercise*, an abnormal augmentation of the cardiac output in regard to the metabolic needs is observed. These findings are similar to those the authors have observed in patients suffering from systemic arteriovenous aneurysms.

IN 1945, Edholm, Howarth and McMichael[4] showed for the first time that the peripheral blood flow was considerably increased in limbs, the bones of which were affected by active osteitis deformans. On this occasion, they reported the findings in a patient suffering from both congestive heart failure and Paget's disease, in whom they found a very high cardiac output: 13.3 liters per minute. They suggested that the increase in the blood flow in the bones was responsible for the high-output state. Since then, Paget's disease has been placed among the clinical conditions which lead to congestive heart failure accompanied by high cardiac output, the other conditions being systemic arteriovenous aneurysm, beri-beri, severe anemia, hyperthyroidism and emphysema.[1, 8, 11]

Edholm, Howarth and McMichael believed that osteitis deformans could give rise to conditions similar to those created by systemic arteriovenous aneurysms and that it is probable that direct communications between arteries and veins exist in the bones of patients with Paget's disease. Though the existence of such fistulas have not been certainly demonstrated,[2] Rutishauser, Veyrat and Rouiller[10] have clearly shown histologically that there is an extremely important increase in the vascularity of the diseased bones. This considerable augmentation in periosteal vascularity has been also demonstrated in vivo and post-mortem by the injection of radio-opaque material.[3, 9, 12] Moreover, an important increase in the size of the vessels forming the periosteal plexus has been demonstrated by dissection.[3] Recently, Howarth[5] has called attention to the presence of a high cardiac output in 5 out of 13 patients with Paget's disease. With the exception of one case in which the cardiac output reached 13.3 liters, the increase of output observed was slight, in particular if one keeps the fact in mind that the observations on these patients were not made under basal conditions. Howarth stated that involvement of 35 per cent of the skeleton by Paget's disease is necessary before an augmentation of cardiac output can be observed; moreover she thought that the disease must be in an active stage, accompanied by a high phosphatase level.

For several years, we have studied the circulatory modifications occurring in Paget's disease. We have observed seven cases. In one patient, the disease affected only the right leg; in another, it involved all bones except those of the right arm; in the last five patients, the disease was generalized. The importance of the alterations varied according to the bones affected. In these patients, we studied the hemodynamic modifications that were present at rest and also during exercise.

RESULTS

We have been able to confirm the existence of a considerable increase in the peripheral blood flow in the limbs affected by the disease. This phenomenon is clearly demonstrated in the patient in whom the disease is localized in the right leg (fig.1). This patient, 70 years old, suffered from congestive heart failure of coronary origin and from emphysema. The arterial oxygen saturation was decreased because of the lung condition (table

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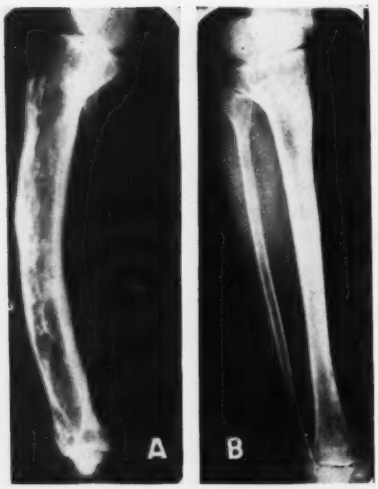

FIG. 1. Osteitis deformans localized in the right leg (A). The left leg is unaffected. (B).

TABLE 1.—*Osteitis Deformans of the Right Leg*

DE CON, Jean, age 70. Congestive heart failure and emphysema

Oxygen content (vol. %)	
Right femoral artery	14.07
Left femoral artery	14.08
Right femoral vein	6.20
Left femoral vein	4.13
Capacity (vol. %)	17.70
Saturation (%)	81
Arteriovenous difference (vol. %)	
Right leg	7.87
Left leg	10.94

TABLE 2.—*Osteitis Deformans. Arteriovenous Oxygen Difference in a Normal Arm and in a Diseased Leg*

Oxygen content (vol. %)	
Arterial	13.85
Left arm vein	5.67
Left leg vein	10.74
Oxygen arteriovenous difference (vol. %)	
Left arm	8.18
Left leg	3.11

1). The arteriovenous oxygen difference was increased in both legs due to cardiac unsufficiency, but was definitely higher in the unaffected leg. In another patient, osteitis deformans involved all bones of the skeleton, except those of the

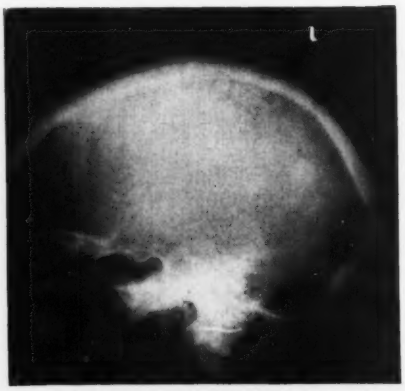

FIG. 2. Skull in Paget's disease affecting the entire skeleton except the right arm.

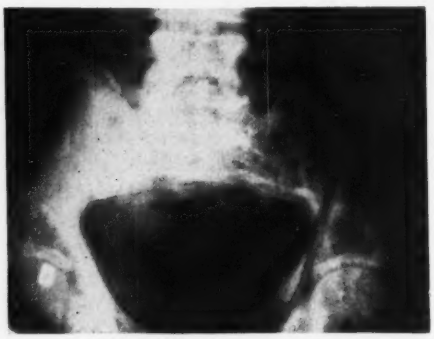

FIG. 3. Pelvis in Paget's disease affecting the entire skeleton except the right arm.

right arm (figs. 2 and 3). In this case, the arteriovenous oxygen difference was considerably lower in one of the diseased legs than in the right arm (table 2). These findings clearly indicate arterialization of the venous blood in the involved limbs.

In the various cases of generalized Paget's disease which we have studied, the cardiac output remained within the limits of normal when the patients were at rest. Two examples of this are shown, in tables 3 and 4. Table 3 shows the hemodynamic data obtained on a patient, age 54, whose cardiac output was 5.72 liters and arteriovenous oxygen difference 4.38 per cent. The pressures in the pulmonary artery and in the cardiac cavities were normal; so also were the vascular resistances and the cardiac work. In another patient whose data are

TABLE 3.—*Paget's Disease. Circulatory Dynamics*
DEG, Jean, age 54

Oxygen consumption (cc. minute)	251
Erythrocytes (cu.mm.)	3,160,000
Hemoglobin (%)	62
Oxygen content (vol. %)	
Femoral artery	13.85
Pulmonary artery	9.47
Capacity (vol. %)	14.9
Saturation (%)	93
Arteriovenous difference (vol. %)	4.38
Cardiac output (L/min.)	5.72
Cardiac index (L/min. M^2)	3.66
Pressures (mm. Hg)	
Capillary	8 (mean)
Pulmonary artery	25/8 (mean 12)
Right ventricle	25/3
Right auricle	3 (mean)
Femoral artery	120 (mean)
Total pulmonary resistances (dynes sec. cm^{-5})	168
Vascular pulmonary resistances (dynes sec. cm^{-5})	56
Right ventricular work (joules min.)	9
Left ventricular work (joules min.)	91

TABLE 4.—*Paget's Disease. Circulatory Dynamics*
DUR, Zélie, age 55

Oxygen consumption (cc. minute)	213
Oxygen content (vol. %)	
Femoral artery	17.93
Pulmonary artery	13.80
Capacity (vol. %)	19.88
Saturation (%)	92
Arteriovenous difference (vol. %)	4.13
Cardiac output (L/min.)	5.18
Cardiac index (L/min. M^2)	3.27
Pressures (mm. Hg)	
Capillary	7 (mean)
Pulmonary artery	35/10 (mean 20)
Right ventricle	35/4 (mean 12)
Right auricle	4 (mean)
Femoral artery	195/110 (mean 140)
Peripheric vascular resistances (dynes sec. cm^{-5})	2106
Total pulmonary resistances (dynes sec. cm^{-5})	310
Vascular pulmonary resistances (dynes sec. cm^{-5})	201
Right ventricular work (joules min.)	14
Left ventricular work (joules min.)	97

reported in table 4, the cardiac output was 5.18 liters and the arteriovenous oxygen difference was 4.13 per cent (fig. 4). The other hemodynamic characteristics were normal

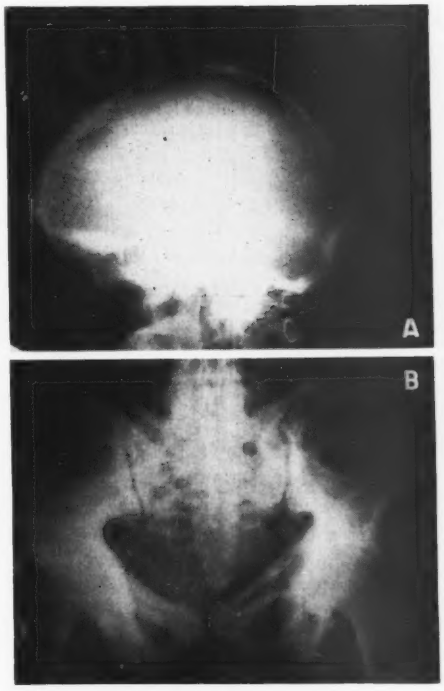

FIG. 4. Skull and pelvis in Paget's disease involving all the bones.

if one takes into account the fact that the patient had an elevated blood pressure.

Briefly then, in patients in whom osteitis deformans was generalized and in whom abnormal arterialization of the venous blood in the limbs was present, circulatory dynamics were practically unchanged at rest. It is thus probable that in these patients a high cardiac output at rest is exceptional, and is to be found only in particularly active forms of the disease. Generally, the increase of the circulation in the pagetoid bones will be insufficient to increase the cardiac output. These facts are similar to those that we have found in patients with systemic arteriovenous fistulas.[6] In man, the cardiac output varies considerably from one patient to the other, in accordance with the importance of the blood flow through the fistula. The same is true in the case of dogs on which we have created fistulas between the femoral vessels. In these animals,

TABLE 5.—*Paget's Disease. Circulatory Dynamics During an Exercise Test*

Cases	O_2 consumption (cc/min.)	Cardiac output (L/min.)	Cardiac index (L/min/M^2)	Pulm. art. press. (mmHg)	Tota. pulm. resist. (dynes sec. $cm.^{-5}$)	Periph. vasc. resist. (dynes sec. cm^{-5})	Cardiac output increase per 100 cc. O_2 (L.)
I. DEG, Jean							
Rest	260	5.72	3.66	25/8 M 12	168	1640	—
Exercise	490	10.90	6.46	28/10 M 13	95	856	2252
II. DUR, Zélie							
Rest	213	5.18	3.27	35/10 M 20	310	2106	—
Exercise	476	8.66	5.48	42/15 M 25	201	1258	1320

arterialization of the right auricular blood varied widely in proportion to the size of the anastomosis: on release of a compressed fistula, the oxygen content of the right auricle varied from 0.54 to 3.26 volumes per cent.[6]

We have also investigated the hemodynamics of our patients during exercise. Two examples are shown in table 5. It is interesting to see that in the course of the exercise, the increase of the cardiac output is abnormally high. While in a healthy person, the cardiac output increases usually from 0.600 to 0.800 liters per 100 cc. of oxygen consumed, one can see that in these two patients, the increase of the cardiac output is respectively 1.230 and of 2.252 liters per 100 cc. of oxygen consumed. Such facts have been established in our various patients suffering from generalized Paget's disease. They suggest that the circulation in the bones affected by Paget's disease increases considerably under effort, and thus enables an important amount of blood to return prematurely to the right heart. These findings are similar to those which we have observed in patients suffering from systemic arteriovenous aneurysms.

SUMMARY

In osteitis deformans (Paget's disease), the peripheral blood flow is increased in the bones affected by the disease. Nevertheless, the increased circulation usually is insufficient to modify significantly the circulatory dynamics of patients studied *at rest.*

On the other hand, during *exercise* an abnormal increase of the cardiac output is observed. This suggests an augmentation of the peripheral circulation in the bones involved by the disease.

It is probable, that important alterations of the hemodynamics are exceptional and will only be found in very severe and active forms of the disease.

SUMMARIO IN INTERLINGUA

In osteitis deformante (morbo de Paget), le peripheric fluxo sanguinee se augmenta in le ossos afficite per le morbo. Nonobstante, le augmento del circulation non suffice usualmente pro modificar de maniera significative le dynamica circulatori del patiente in stato de *reposo.*

Del altere latere, durante *exercitio* un augmento anormal del rendimento cardiac es observabile. Isto supporta le conclusion que il occurre un augmento del circulation peripheric in le ossos que es afficite per le morbo.

Il es probabile que considerabile alterationes hemodynamic es exceptional e se trova solmente in formas severissime e activissime del morbo.

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Rauwolfia Serpentina in the Treatment of High Blood Pressure

A Review of the Literature

By Rustom Jal Vakil, M.D. (Lond.), M.R.C.P. (Lond.)

The root of the *Rauwolfia serpentina* Benth (N. O. Apocyanaciae) has been in use in India for hundreds of years for a host of unrelated ailments. Since 1949, after the English publication of a clinical report by the author on *Rauwolfia serpentina* therapy in fifty cases of essential hypertension, the plant has gained universal acclamation as a useful therapeutic weapon in high blood pressure states. The whole subject of *Rauwolfia serpentina* therapy in hypertension has been reviewed up to the present time, including discussions on the history of the plant, its various species and types, nomenclature, geographic distribution, chemistry, pharmacologic actions and clinical studies, reported on the subject from all over the world.

THE plant rauwolfia is named after the German doctor and traveller Leonhard Rauwolf, who in 1582 published an account of his many travels. Roots of the plant *Rauwolfia serpentina* (Benth) have been recognized in India and the Malay peninsula from ancient times as antidotes to the stings and bites of insects and poisonous reptiles. Mention of the plant is found in an old Hindu manuscript (1000 B.C.)[128] as well as in the monumental works of Charaka (second century, A.D.), under the Sanskrit name of "sarpagandha." It has also been used as a febrifugue, as a stimulant to uterine contractions, for diarrhea, dysentery, insomnia and insanity. For just over two decades, its clinical application has been extended with success to the treatment of high blood pressure.[132]

R. Serpentina or the serpentina plant is a large climbing or twining herb or shrub, belonging to the natural order *Apocyanaceae*, and found in the Himalayas, Assam, Pegu, Java, Tennasserim, Bihar, Deccan peninsula and the Malay peninsula. It is variously known as sarpagandha (from ancient times), chandrika (Sanskrit), chota-chand (Hindi), chand (Bengali), dhan-murua or dhanbarua or pagla-kadawa (Bihar), chandra, chota-chand, karavi or harkai (Bombay), harkaya (Marathi), patala garud or atalagandhi (Telegu), covannamiloori (Tamil), chuvanaavilpori (Malay) and as dhannerna or dhan-barua (Oriya).

Of the 130 odd species of rauwolfia, which are said to occur indigenously in the tropics, Youngken[150] has given an excellent description of the following five, viz. *R. serpentina*, *R. canescens*, *R. micrantha*, *R. densiflora*, and *R. perakensis*. Eight species of rauwolfia grow in India; according to origin or source of supply, it is customary to recognize the Bengal, Bihar, Assam, Dehra Dun and Ceylon varieties of rauwolfia in the Indian market; these show considerable differences in quality and content of the therapeutic alkaloids. The most useful variety of rauwolfia from the therapeutic standpoint is *R. serpentina*, which grows to a height of one and one-half to three feet and has pinkish-white flowers.

Chemical Composition

Early researches suggested the presence in the *R. serpentina* plant of an alkaloid, which was provisionally named psendobrucine. Since 1931, the chemical structure or composition of the plant has been the subject of investigation by numerous observers.

In 1891, Dymock,[43] for the first time detected the presence of an alkaloid and a yellow resin in the root of *R. serpentina*.

In 1931, Sen and Bose[111] found two alkaloids in its root (the total alkaloid content being

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about 1 per cent of the dried root), in addition to fair quantities of resin and starch. Siddiqui and Siddiqui[117] (1931) found, besides phytosterol, oleic acid and unsaturated alcohols, five alkaloids with different physical characteristics and molecular formulae, classified by them into two groups, viz., (1) the ajmaline group of three white crystalline weak bases, ajmaline ($C_{26}H_{26}O_2N_2$), ajmalinine ($C_{20}H_{23}O_4N$), and ajmalicine; and (2) the serpentine group of two yellow, crystalline stronger bases, serpentine ($C_{21}H_{23}O_4N$) and serpentinine ($C_{26}H_{20}O_3N_2$).

In 1932, two Dutch chemists, Van Italie and Stenhauer[137] isolated three alkaloids similar in formula or structure to the ajmaline, ajmalinine and serpentinine of Siddiqui and Siddiqui[117-120]. They named their first alkaloid, rauwolfin ($C_{21}H_{26}O_2N$).

In 1939, Siddiqui[120] reported that the only two alkaloids obtained from the Dehra Dun variety of *R. serpentina* differed from those of the Bihar variety in their chemical structure and melting points and named them isoajmaline or neoajmaline. In 1941, Mookherji[90] isolated an alkaloid from *R. canescens*, and named it rauwolscine ($C_{21}H_{26}O_3N_2$). Muller, Schlittler and Bein,[92] in 1952, isolated a new alkaloid, reserpin, from *R. serpentina*, with an empirical formula of $C_{33}H_{40}O_9N_2$. In 1953, Chowdhury and Ghosh[29] isolated yet another alkaloid, hypotensin, from the serpentina root.

Other alkaloids of *R. serpentina* more recently isolated and described are, sarpagine ($C_{19}H_{22}O_2N_2$), isolated and described by Stoll and Hofmann[123] (1953), raupine ($C_{20}H_{26}O_3N_2$), by Bodendorf and Eder[13] (1953), rauhimbine ($C_{21}H_{26}O_3N_2$), and iso-rauhimbine ($C_{21}H_{26}O_3N_2$) by Hofmann[67] (1954), substance I ($C_{22}H_{26}O_4N_2$) and substance II ($C_{21}H_{25}O_3N_2$) by Popelak and associates[98] (1953) and reserpinine ($C_{22}H_{26}O_4N_2$) by Schlittler and associates[108] (1954).

Pharmacologic Effects

The pharmacologic actions of the *R. serpentina* root and of its individual alkaloids have been investigated from time to time.

On the basis of experiments on frogs, Siddiqui and Siddiqui[117] (1931) showed that while the ajmaline group acts as a general depressant to the heart, respiration and central nervous system, the serpentine group causes paralysis of respiration, depression of nerves and stimulation of the heart. Sen and Bose[111] (1931) reported a small drop of blood pressure, a depression of the heart muscle, respiratory stimulation and relaxation of smooth muscles, in cats and other animals, after the administration of *R. serpentina* alkaloids. Roy[104] (1931) described dulling of sensations, sluggish reflexes and sleep after large doses and death from respiratory failure after lethal doses. In 1933, Chopra and associates,[24] working with the total alkaloids of *R. serpentina* described valuable sedative, hypnotic and hypotensive properties.

In 1940, Hamet[63] observed, for the first time, the sympathicolytic activity of alkaloids, particularly, ajmaline and rauwolfine, isolated from *R. serpentina* (Benth), and remarked on the hypotensive action of several of the alkaloids.

In 1941 and 1942, Chopra and his associates[26, 27] reported exhaustively on the pharmacological and toxic effects of *R. serpentina* root extracts as well as of individual alkaloids; in their experience, while the total alkaloids, alcoholic extracts and serpentine, particularly the last, possess valuable hypotensive properties, ajmaline and serpentinine are hypertensive drugs. Bhatia and Kapur[12] (1944) reported, after the administration in animals of the two alkaloids, isoajmaline and neoajmaline, stimulation followed by depression of the central nervous system, and lowering of the blood pressure in intact, spinal and decerebrate animals, with or without experimentally induced hypertension. In 1944, Gupta, Kahali and Dutt[55] found that the crude resin isolated by Dymock in 1891, also possessed the sedative and hypnotic properties of the serpentina root. Chakravarty[17] (1952) and Mukherjee[91] (1953) described the sympathicolytic effects of the alkaloid rauwolscine, isolated from *R. canescens* (Linn).

Muller and associates[92] (1952) and Bein[8] (1953), on the basis of animal experiments, found the new alkaloid reserpin to possess marked and long-lasting hypotensive, vasodepressor and sedative-hypnotic properties. In

1953, Dasgupta and associates[31] described the sympathicolytic activity and adrenergic blocking activity of the purified total alkaloids and the oleoresinous fraction of *R. serpentina*. In their opinion, the hypotensive action of the root is only partly due to the sympathicolytic effect, other factors like peripheral vasodilatation being also concerned. Chowdhury and Ghosh[29] (1953) reported the hypotensive effects of a new alkaloid, hypotensin, isolated from the root.

On the basis of experimental and clinical studies, the root of *R. serpentina* is said to have the following pharmacologic attributes.[132] (1) By action on the vasomotor center, it leads to generalized vasodilatation, with a lowering of blood pressure. (2) By depressant action on the cerebral centers, it soothes the general nervous system.[145] (3) It exerts a sedative action on the gastric mucosa and a stimulating action on the plain musculature of the intestinal tract. (4) It stimulates the bronchial musculature.

Clinical Studies

Until the year 1949, in spite of many notable clinical and pharmacologic contributions on the subject in India, interest in *R. serpentina* therapy had remained strictly localized to that country.

When, in 1949, the author[132] published in England the first clinical report on *R. serpentina* therapy to appear outside of India, interest in the subject soon became international. Since that time, contributions, both clinical and pharmacologic, on the subject of *R. serpentina*, have been literally pouring forth from different countries of the world.

Earlier Indian Contributions

Although the therapeutic value of *R. serpentina* in cases of insanity, particularly when associated with maniacal tendencies, was recognized in 1931 by Sen and Bose[111] and subsequently confirmed by Ghosh in 1940, the first mention in the literature of its value in human cases of hypertension was in 1940, when Vakil[130] made the following allusion to the subject: "After a trial of this preparation, one finds it useful in a percentage of cases of hypertension only; the indications and suitability of the case for the drug have not as yet been worked out."

A vague reference to the use of a tincture or alcoholic extract of the root of *R. serpentina*, in cases of high blood pressure, was made in 1942 by Paranjpe.[95] He claimed improvement, without any statistical support, in most cases of hypertension; the hypotensive action was said to be particularly gratifying in elderly subjects and in the case of the diastolic pressure.

In 1942, Bhatia,[11] after employing *R. serpentina* in the treatment of cases of high blood pressure, both with and without renal damage, reported it as a useful and well-tolerated hypotensive remedy.

International Contributions

In 1949, in England, Vakil[132] reported the results of an extensive clinical trial of the dried root of *R. serpentina* in 50 cases of essential, benign hypertension. Satisfactory drops of both systolic and diastolic blood pressure levels were observed in 85 per cent and 81 per cent of cases, respectively, after four weeks of therapy; it was concluded, on the basis of this study, that *R. serpentina* has "a definite place in the treatment of high blood pressure."

The following are among the most noteworthy of the international contributions on the subject.

From the United States. In 1953, after carrying out clinical trials in over 100 cases, over periods varying from one month to one year, Wilkins and Judson,[148] found *R. serpentina* useful in lowering high blood pressure levels, nonhabit forming, free of serious side effects, and applicable in most cases of hypertension. In the opinion of Wilkins,[146-149] *R. serpentina* is "a valuable addition to our armamentarium against hypertension," possessing both symptom-relieving and hypotensive properties, especially in young labile hypertensives with sensitive nervous systems. Amongst side effects, he observed nasal stuffiness, a tendency to diarrhea, gain in body weight, nightmares and, on rare occasions, a sense of "depressed anxiety" or jitteriness. Optimal results were obtained with a dose of

100 to 125 mg. of crude root, administered one to three times a day.

In 1953 Ford and Moyer[49], after subjecting 25 cases of essential hypertension to combined *R. serpentina* and hexamethonium therapy, were able to report (1) adequate reduction of pressure levels in a large number of cases, (2) fewer and milder side reactions than with hexamethonium alone, (3) adequate lowering of pressure even with suboptimal doses of hexamethonium and (4) better stabilization of pressure levels.

From England. In 1954, after a trial of *R. serpentina*, used in conjunction with veratrum viride, in 24 severely hypertensive patients, Joiner and Kauntze[71] could not demonstrate either a good therapeutic response to the drug or evidence of synergistic action. Bradycardia and lowering of diastolic pressure were observed in some of their cases, while pruritus and urticaria were noted twice. In view of the acknowledged refractoriness of severe hypertensives to any form of therapy, the disappointing results obtained by these authors are not surprising.

From New Zealand. In 1954 Doyle and Smirk[39] found reserpine, the alkaloid of *R. serpentina*, in large doses (2 to 3 mg., thrice daily), capable of inducing striking falls of blood pressure within four to six hours of administration; unpleasant reactions, like fatigue, drowsiness, depression, shivering, feeling of heat, conjunctivitis, restlessness, nausea, vomiting and diarrhea, were observed after larger doses of the drug. An additive effect was noted in some of the cases treated on combined reserpin-methonium therapy.

From Germany and Austria. After using *R. serpentina* in 25 cases, Vida[138] in 1952 found it effective in all kinds of high blood pressure and superior to other hypotensive agents. Arnold[3] (1952), regarded it as (1) the most effective soothing agent with a centrally effective component known for the autonomic nervous system and (2) a valuable hypotensive agent, particularly for cases of labile hypertension. Seliger[110] (1952), after confirming Vakil's work on the subject, recommended continuous *R. serpentina* therapy in the treatment of high blood pressure. Arnold and Bock[4] (1953), obtained a good hypotensive response in 37 out of 50 cases of hypertension treated with *R. serpentina*. Cerebral arteriosclerosis and nephrosclerosis were regarded as contraindications. Lassitude was commonly noted as a side effect and orthostatic phenomena without circulatory collapse, on rare occasions. Sarre[106] (1953) reported systolic pressure drops of over 30 mm. and diastolic drops of over 15 mm. in the great majority of his cases; headache and vertigo were constantly relieved and subjective improvement noted in almost all the cases. According to Newmayer[94] (1953), *R. serpentina* is capable of lowering the systolic and diastolic pressures in most cases of labile hypertension, in a fair number of cases of fixed hypertension and in occasional cases of renal hypertension. The pressure effect was said to start gradually, attaining its maximum after two or three weeks; while nose blocking was common after therapy, symptoms akin to collapse were rarely observed. The bradycardia was found to be proportional to the degree of pressure drop. Kleinsorge and Wittig[75-76] (1954), after using *R. serpentina* alkaloids in 84 classified cases of hypertension, reported a systolic response in about 40 per cent of cases. While subjective improvement occurred in about two-thirds of his cases, no alterations were observed in the eye grounds, electrocardiographic tracings and renal function tests. In 1953, Marx[85] found the drug useful in all varieties of hypertension, including the nephrosclerotic and cerebral arteriosclerotic forms. He was greatly impressed by its sedative qualities. Meissner[88] (1953) found it effective in 90 per cent of hypertensive cases, normal pressures being restored within three weeks in many cases. An average lowering of 40 mm. Hg of pressure was observed in cases of labile hypertension, of 28 mm. in fixed hypertension and of 15 mm. in renal hypertension. A good response was also noted in hyperexcitable and thyrotoxic individuals. Watschinger[143] (1953) found it superior in many respects to the other better known hypotensive agents. Runck[105] (1954) was impressed by both the hypotensive effect of the drug, as well as by the complete absence of toxic reactions. He advised a modification of dosage in cases of diabetes and

cerebral arteriosclerosis. Klausgraber[74] (1953), in Vienna, tried the drug in 83 cases of hypertension of diverse types; some cases were associated with renal and cardiovascular complications. A satisfactory response of both systolic and diastolic pressures was obtained in 63 per cent of cases. Although all cases were subjectively improved, the electrocardiographic tracings, retinal fields, renal function tests and teleradiograms remained unaffected by the treatment.

From Switzerland. In 1953 Loffler and associates[83] tried the alkaloid reserpin, isolated from *R. serpentina* by Swiss workers, in 51 cases of hypertension. Adequate falls of pressure were observed in only 14 cases and maintained for only 12 days in spite of continuation of therapy. Subjective improvement was reported in 16 cases, and side effects, including fatigue, depression, excitability, painful extremities, visual phenomena, miosis and dryness of mucous membranes only in cases treated with doses larger than 1.5 mg. per day.

From Japan. In 1954 Goto[52] found the alkaloid reserpin effective in 12 out of 15 cases of hypertension. The hypotensive action was apparent three to seven days after initiation of therapy and maintained for 10 to 21 days after its suspension. Nose block and "pharyngeal bolus" were observed in three cases. On trying various combinations of *R. serpentina* with veratrum viride and Apresoline in 72 cases of hypertension, including 13 cases of renal hypertension, Goto obtained a hypotensive response of 30 mm. or over within a month of the initiation of therapy in 85 per cent of cases; this result was maintained for two to four months. Apart from occasional vertigo and conjunctivitis, there were no side-reactions.

From India. In 1952, Chakravarty and associates[17] reported average systolic and diastolic pressure falls of 18.5 mm., and 16.4 mm., respectively, on the tenth day of *R. serpentina* therapy. Mazumdar and Mukherjee[86] (1951) reported subjective improvement in all cases and a hypotensive response in 7 out of 12 cases of hypertension. Chowdhury and Ghosh[29] (1953), found the alkaloid "hypotensin", isolated from *R. serpentina* in Calcutta, effective, even in small doses, in most cases of hypertension, and without ill effects. In 1953 Vakil[133] reported a good hypotensive response to the alkaloid reserpine in 72 per cent of cases, and few side effects. The accidental administration of 10 times the therapeutic dose to one patient merely resulted in a transitory feeling of lassitude and vertigo.

Many more studies, hitherto unpublished, on the hypotensive action of *R. serpentina* root or of its individual alkaloids, either used singly or in combination with hypotensive agents like veratrum viride, hexamethonium and hydralazine, have been brought to light recently, from various parts of the universe. The results are said to be uniformly good in mild and moderate cases of hypertension and devoid of any serious or toxic ill effects. As far as can be ascertained, the results obtained with individual alkaloids of *R. serpentina* have not differed materially from those obtained with the crude extracts of the root.

Present Day Status of *R. Serpentina* Therapy

In the short span of about 15 years that the dried root of *R. serpentina* has been on the market in India, this hypotensive remedy has gained such unprecedented popularity that the following statements can be made: (1) There is hardly one patient with high blood pressure in that country who has not been subjected at some time or another to its application[132]. (2) In the experience of over 90 per cent of Indian doctors, as revealed by a questionnaire circulated by Vakil in 1949,[132] *R. serpentina* is the best "hypotensive" remedy known. (3) One manufacturing firm alone claims to have sold, prior to the year 1954, over 98 million tablets of the dried root, of *R. serpentina*.[16] (4) Shipments of the serpentina root in crude or tablet form have been sent from India to over 17 countries of the world within the last four years.[16] (5) It is said to be prescribed by over 60,000 physicians at the present time.[16]

R. Serpentina: Crude Extracts Versus Pure Alkaloids

For many years now, and particularly after the isolation of the alkaloid, reserpine, a strong

ontroversy has been raging between opposing chools of thought about the relative merits or uperiority of the one form of *serpentina* reparation over the other.

The following arguments have been put orward in favor of the alkaloid: (1) Being a ure crystalline single alkaloid, it cannot roduce undesirable effects from unknown lkaloids in the whole root. (2) Being a single nown entity, results are likely to be more redictable. (3) Much smaller doses are equired to obtain the same results. (4) According to some observers, it is a much more potent hypotensive agent.

Those who report favorably on the whole extract in preference to alkaloids support their claims with the following arguments: (1) The whole extract of *R. serpentina* contains not one but several proved alkaloids with hypotensive properties, ajmaline, serpentine and ajmalinine. According to those of this school of thought, the only pressure-raising alkaloid in the whole extract is serpentinine, which is more than neutralized by the hypotensive alkaloids. (2) Alkaloids are not the only active constituents of *R. serpentina* root, the yellow resin fraction being also a highly active, sedative agent, as first noted by Dymock[42] in 1891, and subsequently confirmed by Gupta, Kahali and Dutta[55] (1941). (3) Numerous authorities in the past have reported the therapeutic superiority of the crude extract[111, 26, 144]. (4) The synergistic action of the total alkaloids eliminates danger of hypersensitivity likely to develop from the use of single alkaloids.

Summario in Interlingua

Es presentate un revista del litteratura in re *Rauwolfia serpentina* como agente hypotensive, includente referentias a 151 distincte contributiones. Introductorimente le autor summarisa le historia ancian e plus recente del planta, su usos in medicina popular, su characteristicas botanic, e su ecologia.

Recercas chimic in re le agentes efficace in *R. serpentina* es describite ab lor initio in le discoperta per W. Dymock in 1891 que le planta contine un alcaloide.

Le studio scientific del effectos pharmacologic de *R. serpentina* es traciate ab 1931 al presente. Le nunc recognoscite usos del planta es enumerate sequentemente: (1) Per ager super le centro vaso-motor, illo produce vasodilatation generalisate con resultante effectos hypotensive. (2) Per su action depressive super le centros cerebral, illo calma le systema nervose general. (3) Illo exerce un effecto sedative super le mucosa gastric e un action stimulante super le nonstriate musculatura del tubo digestive. (4) Illo stimula le musculatura bronchial.

Studios clinic ante le anno 1949 esseva restringite a India. A ille tempore le autor del presente articulo publicava un articulo in Anglaterra que initiava un longe serie de studios e reportos. Istos es summarisate in gruppos secundo le paises de lor origine. Le revista include contributiones ab le Statos Unite, Anglaterra, Nove Zelanda, Germania, Austria, Switza, Japon, e evidentemente India.

Le section concludente del articulo discute le stato presente del therapia a *R. serpentina*. Es presentate le major argumentos del autoritates qui prefere le extracto crude e le major argumentos de illes qui prefere le alcaloides in forma pur.

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Atypical Tetralogy of Fallot: A Noncyanotic Form with Increased Lung Vascularity

Report of Four Cases

By RICHARD D. ROWE, M.B., M.R.C.P. (EDINBURGH), PETER VLAD, M.D. AND JOHN D. KEITH, M.D.

Only recently has the association of pulmonic stenosis with increased pulmonary blood flow been recognized. Four symptomatic infant cases are described in which the clinical diagnosis was large interventricular septal defect. Hemodynamic study showed the presence of associated pulmonic stenosis. Features suggesting that there is an overriding aorta in these patients, and that they, therefore, form an atypical group within the tetralogy of Fallot, are presented. The diagnosis has been confirmed in one case at autopsy. Their differentiation from clinically similar malformations as well as the surgical problem they pose is discussed.

ACCURATE DIAGNOSIS of cardiac malformations frequently requires special studies in any age group, but particularly is this so in young subjects. Nowhere is the fact better demonstrated than in a group of infants presenting, with cardiorespiratory symptoms, a harsh systolic murmur and thrill over the lower precordium and pulmonary plethora.

The picture of a large, isolated ventricular septal defect in infancy has been well described.[1-3] The malformation is characterized by failure to thrive, frequent respiratory infections, a harsh systolic murmur and a thrill over the lower left precordium, accentuated or obscured second pulmonic sound, cardiac enlargement with increased lung vascularity, combined ventricular hypertrophy in the electrocardiogram and often congestive heart failure.

While the clinical features[4-7] and results of accessory investigations[8-12] in the tetralogy of Fallot are now universally known, variations of the malformation in infancy have not been widely discussed.[13] Although central cyanosis and normal heart size with clear lung fields are the chief diagnostic points in any age group, there are not infrequent exceptions to these criteria in the young baby. Taussig established that cyanosis may be delayed in its appearance in the infant case, a fact she attributes to patency of the ductus arteriosus. In our experience at the Toronto Hospital for Sick Children,[14] one-third of the patients with this malformation were cyanotic at birth and a further one-third by six months of age. The remainder developed cyanosis at variable periods up to several years of age, a very few cases being clinically always acyanotic at rest. The cardiac murmur is usually systolic in time and in 75 per cent is maximal over the left lower precordium. While it is more difficult to be certain about splitting of the second basal sound in infants, it is unusual to detect other than a single sound in this region. Right ventricular hypertrophy in the electrocardiogram is the rule. Such abnormality may be recognized in even the very young infant.[15] Rarely, left ventricular hypertrophy or combined ventricular hypertrophy has been recorded.[16, 17] Radiological findings vary. Some hearts certainly appear normal in size and shape, some have a slight pulmonary bay, but many bizarre contours and even enlarged hearts may be seen, especially in the first year.[14] The association of a right aortic arch is suggestive but by no means conclusive evidence of the tetralogy, as it occurs in infants

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with other cyanotic defects such as truncus arteriosus and tricuspid atresia.[18, 19] Whereas in the older child with tetralogy, the lung vascular markings are reduced, they more often appear normal in infants. Usually the only occasions where markedly increased vascular markings will be seen in this malformation are in some cases with increased collateral flow to the lungs via enlarged bronchial arteries[20] or in cases of unilateral pulmonary artery atresia.[21, 22] In both these variants the patient is most often obviously cyanotic and the full development of the former type is uncommon in infancy. In infants, then, though a case of tetrad may be noncyanotic clinically and have a cardiac murmur suggestive of ventricular septal defect, marked increase in lung vascularity in association with obvious congenital heart disease has been regarded as sufficient to exclude this malformation.

Nevertheless, it has been recently recognized that pulmonary stenosis may be associated with increased pulmonary blood flow.[23-31] This occurs when, for example, pulmonary stenosis with normal aortic root is complicated by ventricular septal defect.[24, 26-28, 30, 31] From the latter reports emerges the clinical picture of a noncyanotic older child or adult, free of any cardiac or respiratory symptoms, with a harsh systolic murmur in the lower precordium accompanied by a thrill. The second basal heart sound may be single or split. X-ray films reveal slight, if any, cardiac enlargement, a pulmonary artery segment bulge and slight pulmonary plethora. The electrocardiogram, though sometimes normal, more often reveals moderate right ventricular hypertrophy or incomplete right bundle branch block. Physiologic studies show moderate pulmonic stenosis frequently, but not necessarily, systemic systolic pressure levels in the right ventricle, a moderate-volume left-to-right interventricular shunt and only rarely any venoarterial shunt with exercise.

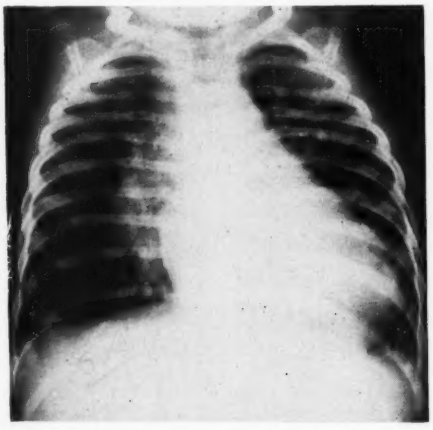

FIG. 1 Case 1. Six foot film of chest showing cardiac enlargement, right aortic arch and increased lung vascularity.

Recently we have encountered four noncyanotic infants with the clinical features of a large ventricular septal defect in whom further studies suggested the diagnosis, of tetralogy of Fallot of an atypical type.

CASE REPORTS

Case 1. J. M., a 6-month old white male, was found to have a heart murmur soon after a normal

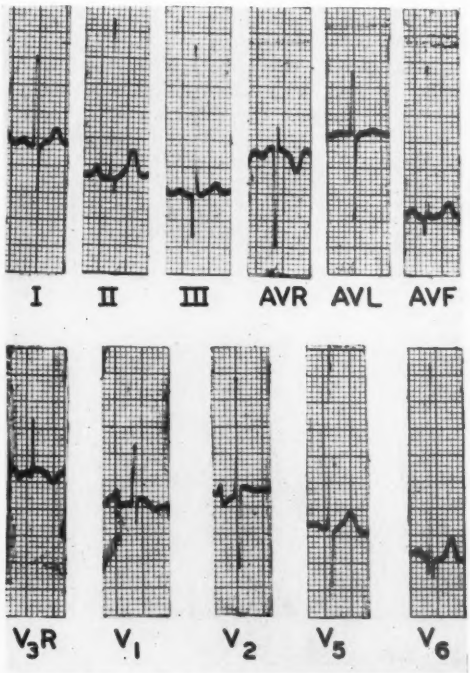

FIG. 2. Case 1. Electrocardiogram. Normal electrical axis, left auricular hypertrophy and combined ventricular hypertrophy. The voltage of R in the left precordial leads suggest that the left ventricle is more hypertrophied than the right.

TABLE 1.—*Results of Cardiac Catheterization*

Case	Age	O_2 Saturation					Pressure mm. Hg			
		VC	RA	RV	PA	SA	RA	RV	PA	SA
1 J. M.	6 mos.	60†	53	86	NK	93‡	3	75/5	25/10	75/40‡
2 A. S.	7 mos.	58*	70	88	77	93	7	100/5	10/−5	95/70
3 S. K.	4 mos.	42*	47	75	77	94.5‡	5	95/5	20/5	90/75‡
4 M. F.	30 mos.	68†	61	86	88	97.5‡	5	75/10	35/15 Wedge: 10	75/50‡

* Superior vena cava.
† Inferior vena cava.
‡ Aorta. VC Vena cava, RA Right auricle, RV Right ventricle, PA Pulmonary artery, SA Systemic artery.

birth. He failed to gain well and suffered from frequent respiratory infections. Cyanosis had not been noted. The physical examination revealed a thin, noncyanotic infant weighing 13½ pounds. There was no evidence of heart failure, although the respiratory rate was increased. A grade V tearing systolic murmur was heard maximally at the fourth left intercostal space and accompanied by a systolic thrill. The second pulmonic sound was accentuated and split. The blood pressure was 100/55.

The cardiothoracic ratio (CTR) by roentgenogram (fig. 1) was 0.60. Fluoroscopy showed a rather straight left border to the heart and a right aortic arch. The lung vasculature was markedly increased and slight intrinsic pulsations were visible. Enlargement of the left auricle was evident on examination with barium.

The electrocardiogram (fig. 2) had an axis of QRS of about +60 degrees. Left auricular and combined ventricular hypertrophy were present.

Cardiac catheterization was performed on Feb. 2, 1954 (table 1). The cardiac catheter was passed readily from the right ventricle into both the ascending aorta and the main and right pulmonary arteries. A tracing recorded during withdrawal from the pulmonary artery to the right ventricle showed valvular pulmonic stenosis. The arterial oxygen saturation estimated by ear oximetry was 98 per cent at rest with no change on crying.

A venous angiocardiogram (fig. 3) showed normal size and position of the pulmonary artery. No clear cut evidence of pulmonic stenosis was shown by this examination. The aorta opacified normally from the left ventricle in the late films.

Case 2. A. S., a 7-month old white male, was found to have a heart murmur at birth. Frequent respiratory infections with dyspnea and stridor had been a problem. Cyanosis had not been noted. The physical examination revealed a thin, noncyanotic infant weighing 11½ pounds. There was no evidence of heart failure but a rapid respiratory rate and moderate stridor were present. A grade V systolic murmur with thrill was located maximally at the fourth left intercostal space. The second pulmonic sound was reduced and single. The blood pressure was 100/70.

The cardiothoracic ratio by roentgenogram was 0.57. Fluoroscopy showed no distinct pulmonary artery bulge and a left aortic arch. The lung vasculature was increased and minimal intrinsic pulsations were visible in the right lung. Left auricular size was normal as judged by barium swallow.

The electrocardiogram had an axis of QRS of about +75 degrees. There was evidence of combined ventricular hypertrophy.

Cardiac catheterization was performed on May 7, 1954 (table 1). The cardiac catheter was passed into the right pulmonary artery and a withdrawal pressure from this vessel to the right ventricle showed a combined valvular and infundibular

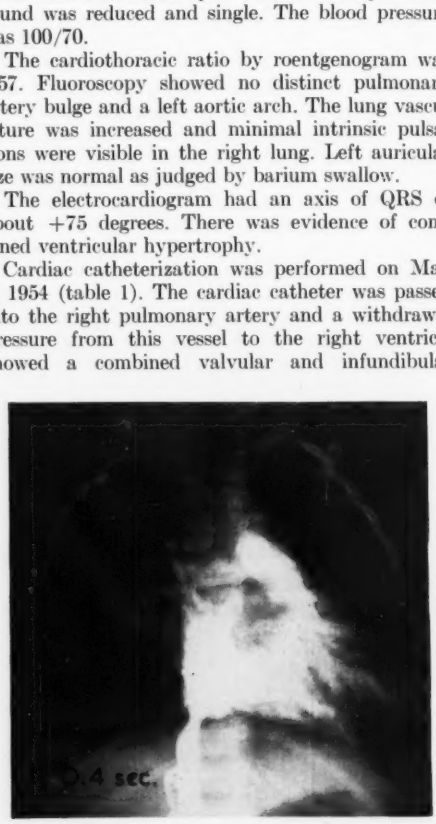

FIG. 3. Case 1. Venous angiocardiogram. Anteroposterior film at 0.4 second following injection of contrast material. There is good filling of normal size pulmonary arteries, absence of clear cut evidence of pulmonic stenosis and no evidence of aortic filling. Later films showed a large left atrium and an aorta filling from the left heart.

stenosis to be present. The aorta was not entered from the right ventricle. The arterial oxygen saturation, estimated by ear oximetry, was 93 per cent at rest and 95 per cent with crying.

Angiocardiography was not performed in this patient.

Case 3. S. K., a 4-month old white female, was said to have been cyanosed briefly at birth when a heart defect was recognized. Because of frequent respiratory tract infections and failure to thrive, she was referred for further investigation of her malformation. The physical examination revealed a markedly dystrophic, non-cyanotic infant weighing 8½ pounds. There was no evidence of heart failure but the respiratory rate was increased at rest. A coarse, to and fro murmur was audible in the pulmonic area. A systolic thrill was palpable in the third left intercostal space. The second pulmonic sound was accentuated and splitting was not detected. The blood pressure was 90/75.

The CTR by roentgenogram (fig. 4) was 0.56. Fluoroscopy showed an elevated apex and a full left middle arc. A small left sided aortic arch was visible on barium swallow. The lung vasculature consisted in the right hilus of a dense pulsating mass, but the left sided vascularity was obscured by the cardiac shadow. The left auricle was not notably enlarged on barium swallow.

The electrocardiogram (fig. 5) showed an axis of QRS of +120 degrees. In the right precordial leads marked right ventricular hypertrophy with added right auricular dilatation was evident from the qR pattern present. The presence of Q waves in the left chest leads in the presence of right ventricular hypertrophy was considered to be evidence of associated left sided hypertrophy.

Cardiac catheterization was performed on April 27, 1954 (table 1). The cardiac catheter was passed both medially into the ascending aorta and from the outflow tract of the right ventricle into the main

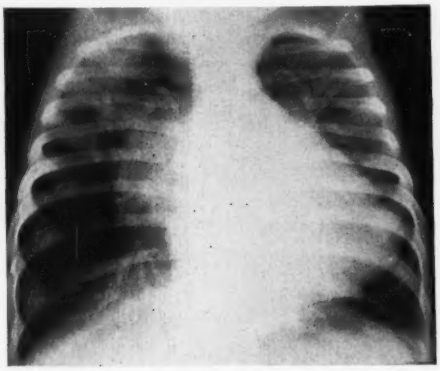

FIG. 4. Case 3. Six foot film of chest showing light cardiac enlargement with increased lung vascularity, particularly noticeable on the right.

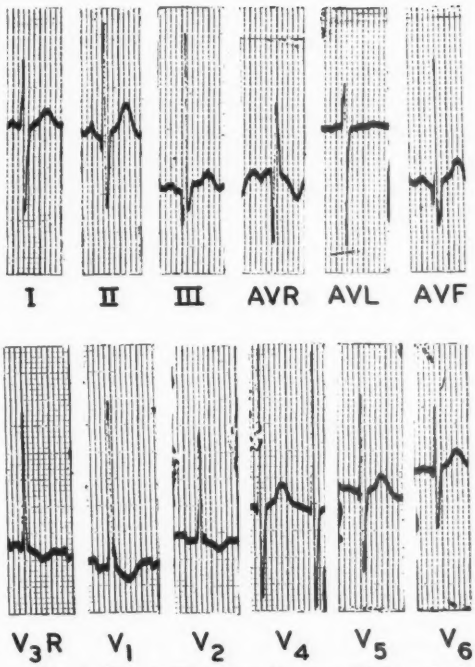

FIG. 5. Case 3. Electrocardiogram. Right axis deviation, marked right ventricular hypertrophy and possible associated left ventricular hypertrophy of a lesser degree.

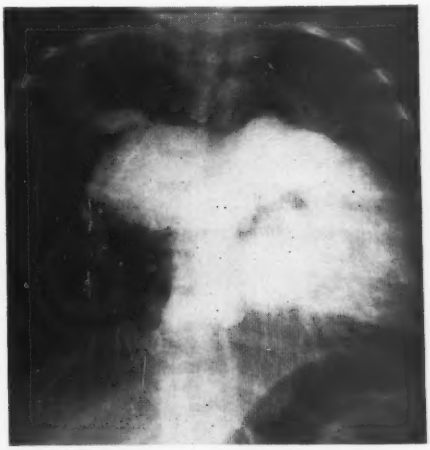

FIG. 6. Case 3. Venous angiogram. Contrast material present in the right auricle and right ventricle which shows a wide outflow tract and a dome stenosis of the pulmonary valve. There is aneurysmal dilatation of the right main branch. At first appearance this suggests absence of the left branch of the pulmonary artery but close examination reveals a hypoplastic left branch. Note absence of aortic filling.

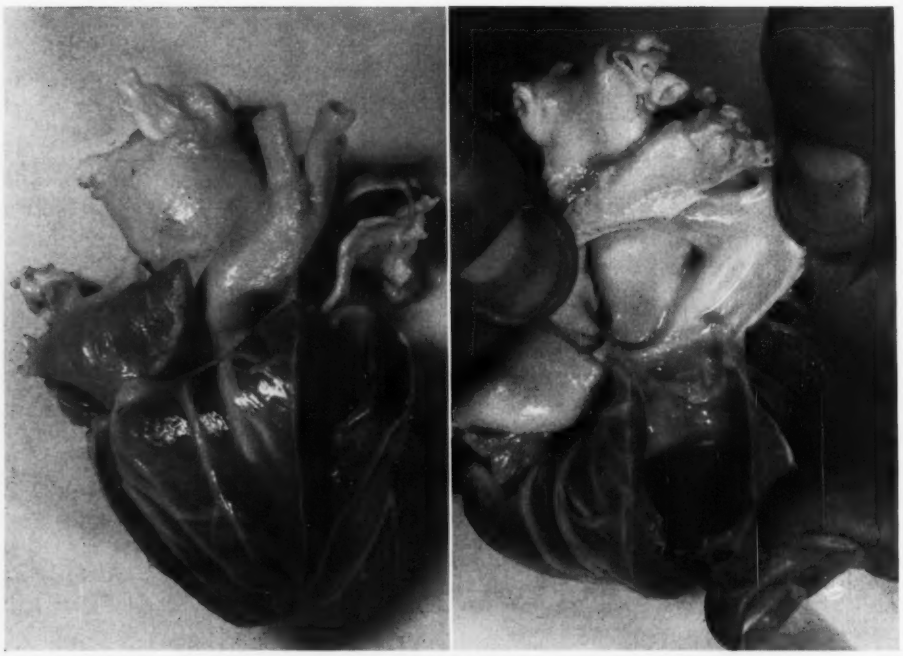

FIG. 7. The heart in case 3: a) frontal view showing the markedly dilated infundibulum, narrow pulmonic ring and the large right branch of the pulmonary artery. b) The main trunk of the pulmonary artery is exposed to demonstrate the narrow pulmonic ring and the two rudimentary valve cusps.

pulmonary artery. A withdrawal pressure tracing from the latter vessel demonstrated valvular pulmonic stenosis. A dye dilution curve from the right ventricle failed to show evidence of right-to-left shunt and was consistent with the large volume left to right shunt. The arterial oxygen saturation, estimated by ear oximetry, was 97 per cent at rest and on crying.

A venous angiogram (fig. 6) revealed valvular pulmonic stenosis, an aneurysmal trunk and right main branch of the pulmonary artery with an apparently hypoplastic left branch. A hypoplastic aorta opacified in the late films.

This infant suffered repeated pulmonary infections over the next nine months and died from bronchopneumonia at 13 months of age. At autopsy (fig. 7), the heart weighed 95 Gm. The systemic and pulmonary venous connections were normal. The aorta was dextroposed, arising approximately 50 per cent from each ventricle. The internal circumference of the ascending and descending aorta was 32 mm. and 19 mm., respectively. The aortic arch and descending aorta lay on the left side of the spine. The pulmonary artery arose normally from the right ventricle and externally there was an obvious constriction at the pulmonic ring. The internal circumference of this ring was 20 mm. The main trunk was a short, narrow vessel giving rise to the main branches. These were of aneurysmal dimensions, the internal circumference of the left branch being 50 mm. and the right 70 mm. These aneurysmal branches ended bluntly at the hili. Very small vessels, approximately 4 mm. in diameter, entered the lungs as offshoots of the main branches. Two slightly prominent ridges, crescentic in shape, with the concavity directed upwards, marked the expected site of the pulmonary valve. There were no cusps as such, numerous irregular nodules being present in their place. These rudimentary structures left the valve ring unguarded. The aortic, mitral and tricuspid valves were normally formed. The ductus arteriosus and foramen ovale were closed. The left auricle was markedly dilated, being three times larger than the right. The right ventricle was thick walled (8 mm.) and there was no evidence of infundibular stenosis. On the contrary, the outflow tract of this chamber was very large. The left ventricle was capacious, being twice as large as the right but was not thick walled (5 mm.). The ventricular septal defect measured 13 by 7 mm.

Case 4. M. F., a 2½ year old white female, was discovered to have a cardiac defect at 6 months of age when examined during a respiratory infection.

She failed to thrive and became dyspneic after effort from the age of 14 months. Physical examination revealed a thin, non-cyanotic infant weighing 21 pounds. There was no evidence of heart failure and no dyspnea at rest. A harsh grade V systolic murmur, maximal over the fourth and fifth left intercostal spaces, was accompanied by a thrill in this position. The second pulmonic sound was accentuated and closely split. The blood pressure was 110/80.

The cardiothoracic ratio by roentgenogram was 0.65. Fluoroscopy showed a moderate pulmonary artery bulge and a left aortic arch. The lung vasculature was markedly increased and pulsating. Enlargement of the left auricle was detected on barium examination.

The electrocardiogram showed an axis of QRS of ±0 degrees. Combined ventricular hypertrophy was present.

Cardiac catheterization was performed on Sept. 8, 1954 (table 1). The cardiac catheter was passed from the right ventricle both medially into the ascending aorta and via the outflow tract to the right pulmonary artery. A withdrawal tracing from the latter vessel to the right ventricle showed an infundibular stenosis, the pressure in the infundibular chamber being 35/5. A selective ether test from the right ventricle was inconclusive with 0.2 cc. and positive with 0.3 cc. of ether. The arterial oxygen saturation, estimated by ear oximetry, was 95 per cent at rest and on crying.

A selective angiocardiogram from the right ventricle revealed a distinct infundibular stenosis and large, well filled pulmonary arteries with a normal pulmonic valve. The left auricle was enlarged in the late plates, while the aorta filled normally from the left ventricle.

Discussion

These four cases are strikingly similar. All young, noncyanotic infants, they have been plagued with lower respiratory infections from birth; seemingly their major handicap. Failure to thrive is a feature, all being dystrophic at the time of the study. The systolic murmur is localized to the left lower sternal border in three cases, a thrill being palpable at this site in all four patients. Splitting of the second sound in the pulmonic area is present in two cases. There is no evidence of heart failure, although an increased respiratory rate suggested increased pulmonary blood flow. Roentgenographically there is slight to moderate cardiac enlargement, marked pulmonary plethora in all four and a right aortic arch in one case. The electrocardiograms showed a normal axis in two instances and combined ventricular hypertrophy in all. From a clinical viewpoint all four might well be accepted as cases of ventricular septal defect of generous size. The only suspicion that this would not be the sole abnormality was the presence in case 1 of a right aortic arch, Keith[3] having found only one instance of this association in 400 cases of ventricular septal defect.

Cardiac catheterization showed pulmonic stenosis, systemic systolic pressure levels in the right ventricle and a large left-to-right interventricular shunt. Although the aorta was entered from the right ventricle in three instances, the arterial oxygen saturation was normal in all cases and in only one case, where a positive selective ether test was obtained from the right ventricle, was there any evidence of right-to-left shunt. Outputs and flows were not determined, but it is almost certain that pulmonary blood flow is much increased in all patients. The systolic pressure gradient between the right venticle and pulmonary artery ranges from 40 to 90 mm.Hg in these cases. This is a distinctly greater difference than in the so-called "relative" stenosis sometimes present in isolated septal defects. It also exceeds the difference encountered by Rudolph and coworkers[31] in a case of atrioventricularis communis exhibiting a pressure gradient during life but with no organic pulmonic stenosis at autopsy. We therefore feel that our cases may fairly be classed as organic stenoses and that the presence of isolated interventricular communication is excluded.

Angiocardiograms in three instances showed normal sized or enlarged pulmonary arteries, considerable dilution of the contrast medium in the right ventricle in one case, and aortic filling in all at least a full second after pulmonary artery opacification. In only two cases (3 and 4) was the site of pulmonary stenosis well demonstrated by this method. Moreover, by angiocardiography noncyanotic forms of basically cyanotic malformations such as a single ventricle with large pulmonary arteries or even complete transposition of great vessels were excluded.

A ventricular septal defect with pulmonic stenosis is not in doubt. The question remaining

is whether the aortic root is normally placed or overrides the septum. Moffitt,[27] Campbell[28] and Sell[36] have raised this problem in the discussion of several of their cases of pulmonary stenosis with ventricular septal defect. Selzer's studies[32, 33] into the size of isolated ventricular septal defects and their relationship to anatomical aortic overriding have shown how difficult it may be pathologically as well as clinically to differentiate this very point.

The equality of systolic pressures in the right ventricle and systemic circuit favors aortic override although there are admitted fallacies to this interpretation. Probing of the aorta from the left ventricle after passage of the catheter tip through a simple ventricular septal defect is possible, but in infants at least it is much more common to enter the aorta from the right ventricle through an anatomical override. One older case where the aorta was thought to have been probed via the left ventricle[24] eventually was proven to have the tetrad at autopsy. The site of pulmonic stenosis is, in our opinion, of no real assistance in separating the two malformations. In one of our cases,* the association of right aortic arch favors tetralogy of Fallot. It is generally agreed that the combination occurs in about 25 per cent of all cases of the tetrad, whereas in simple pulmonic stenosis with normal aortic root, right aortic arch is extremely rare. Campbell[28] detected only one instance in his 75 cases. We have not found a right aortic arch in 100 cases and, to our knowledge, there has been no report of an autopsy-proven case.

Bouchard and Cornu[34] have recently demonstrated in cases of pulmonic stenosis a characteristic appearance of the right ventricular pressure pulse similar to that previously noted under experimental conditions by Fineberg and Wiggers.[35] In simple pulmonic stenosis of all grades of severity there is a delayed ascent during the period of isometric contraction, an absence of the ejection phase plateau and a delayed fall in pressure giving a symmetrical pointed tracing which differs strikingly from a left ventricular curve in the same patient. On the other hand, in tetralogy of Fallot the form of the right ventricular pressure curve is normal and identical with that obtained from the left ventricle. In two of our patients (cases 1 and 4), where the undamped right ventricular pressure curve recorded at fast chart, speed can be studied in detail, the form taken is normal. This suggests that an anatomical override is present in these cases. Records of the right ventricular pressure in two other personal cases of pulmonic stenosis with ventricular septal defect show that the addition of ventricular septal defect to pulmonary stenosis with normal aortic root need not affect the characteristic ventricular pressure curve found in the isolated condition.

In one patient (case 3) the diagnosis of tetralogy of Fallot made after cardiac catheterization was proven correct at a subsequent autopsy. The degree of aortic override was considerable and little different from the classical case of the malformation. The atypical anatomical features confined to the pulmonary artery were the aneurysmal size of its main branches, the constricted pulmonic root and the rudimentary pulmonic valve. The latter obviously permitted pulmonary regurgitation (suspected in life by the diastolic murmur in the pulmonary area), in addition to the obstructive element resulting from the narrow pulmonic ring. From the clinical findings it seems unlikely that pulmonary insufficiency is present in the other three patients.

If the remainder are in fact variants of the tetralogy of Fallot, they probably have only moderate pulmonic stenosis and this likely constitutes the significant deviation from the more usual form of the malformation. While in one the diagnosis has been established, the remainder await pathological confirmation.

* Two further cases not included in this analysis have been encountered with the same clinical picture in whom investigations are incomplete. These are both dystrophic, noncyanotic infants under 1 year of age with harsh systolic murmurs in the fourth left intercostal space accompanied by a thrill, slightly split second basal sound, absence of congestive failure, moderate cardiac enlargement, increased lung vascularity, *right aortic arch*, combined ventricular hypertrophy in the electrocardiogram and normal arterial oxygen saturation by oximetry at rest and crying. One has been denied further study. The other had cardiac catheterization which shows the same hemodynamic features as the four cases in table 1. The aorta was probed from the right ventricle but the pulmonary artery could not be entered. A venous angiogram is suggestive but not conclusive of valvular pulmonic stenosis.

Apart from academic distinctions, they present a practical problem in several ways. It seems unlikely that these infants will follow the benign course described in pulmonic stenosis with normal aortic root and ventricular septal defect. Follow-up is limited to between 6 and 14 months in our cases. Case 3 died of bronchopneumonia at 13 months, weighing 10½ pounds, after prolonged hospitalization from almost continual lower respiratory infections. Cases 1 and 2 have continued to have frequent attacks of pneumonia requiring hospitalization, despite attempts at prophylactic chemotherapy in one instance. Only case 4 has remained well in the interval. Whatever the true anatomy, these infants at the moment behave more like cases with large isolated ventricular septal defect than pulmonary stenosis. Accordingly the main medical problem is one of treating the recurrent episodes of pulmonary infection and endeavouring to support the infants through the obviously critical first years in the hope that ultimately surgery may relieve them. Sell and coworkers[36] have described a similar clinical picture resulting *after* surgical correction of pulmonic stenosis in very mild cases of tetralogy of Fallot. Anastomotic procedures would therefore seem contraindicated and valvotomy or infundibulectomy at this stage unwise because of the removal of a relative safeguard to pulmonary vasculature. More hopeful might be the closure of the ventricular defect under direct vision combined with valvotomy or infundibulectomy.[37]

Summary

Four infants apparently suffering from large isolated ventricular septal defects are presented in detail.

Accessory investigations showed that these infants have moderate pulmonic stenosis, a large ventricular left-to-right shunt, right ventricular hypertension equalling systemic systolic level and normal arterial oxygen saturation both at rest and with exercise.

It is suggested that these infants may be variants of the tetralogy of Fallot on the basis of the above findings, catheter entry into the aorta from the right ventricle, the contour of the right ventricular pressure pulse in two cases, and the association in one patient of a right aortic arch. In one infant the diagnosis was confirmed at necropsy, nine months after hemodynamic study.

The clinical resemblance in infancy of these cases, large isolated ventricular septal defects and pulmonic stenosis with normal aortic root plus ventricular septal defect is emphasized.

The available surgical procedures for the relief of the tetralogy of Fallot are not indicated in these cases. In the development of therapy for these children primary emphasis should be placed on the correction of the ventricular septal defect.

Summario in Interlingua

Es presentate un detaliate reporto del casos de 4 infantes qui apparentemente suffre de large isolate defectos septal ventricular.

Investigationes accessori demonstrava que iste infantes ha moderate grados de stenosis pulmonar, un large derivation ventricular ab le sinistra verso le dextera, hypertension dextero-ventricular equal al nivello systolic in le circulation major, e normal saturation oxygenic in le arterias tanto in reposo como etiam post exercitio.

Super le base del supra-mentionate constatationes nos concludeva que il se tracta hic de variantes del tetralogia de Fallot. Iste interpretation se trovava supportate per catheterisation del aorta via le ventriculo dextere, per le contorno specific del pulso pressional ventricular que esseva observate in 2 casos, e per le copresentia in un caso de un arco dextero-aortic. Confirmation necroptic del diagnose esseva obtenite in un caso, 9 menses post le studio hemodynamic.

Nos sublinea le similaritate clinic de iste casos in le stadio infantil con le manifestationes de large isolate defectos septal ventricular e de stenosis pulmonar con normal radice aortic plus defecto septal ventricular.

Le application del methodos chirurgic que es normalmente disponibile pro le alleviamento de tetralogia de Fallot non es indicate in casos del genere hic describite. In le elaboration del therapia pro tal patientes infantil on debe preoccupar se de corriger le defecto septal ventricular.

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Lumbar Sympathectomy in the Treatment of Hypertensive Ischemic Ulcers of the Leg (Martorell's Syndrome)

By J. Palou, M.D.

Hypertensive ischemic ulcer (Martorell's syndrome) is an infrequent complication of hypertensive disease. The ulcers appear on the leg as necrotic areas. The pathogenesis is described as ischemia resulting in local gangrene due to obliterating lesions in the arterioles. Actual pathological sections were studied which showed hyaline degeneration between the endothelium and internal elastic lamina, and these changes are similar to those found in other localities in hypertensive patients. Lumbar sympathectomy results in healing of the ulcers.

IN SOME patients with diastolic arterial hypertension, painful ulcers appear on the anterolateral aspect of the leg. These are called hypertensive ulcers and the condition is termed Martorell's syndrome because, in 1945, he first described the condition and presented four cases.[1] Valls Serra reported the first case in a man.[2] Hines and Farber of the Mayo Clinic confirmed the existence of these ulcers and published additional clinical cases.[3] Oller Crosiet devoted a paper to this syndrome[4] and Wright described the second case in a male subject.[5] Recently several papers have confirmed the existence, etiology and clinical characteristics of the hypertensive ulcer.[6-10] Oller-Crosiet and myself jointly reported one case, in 1953.[10]

The ulcer is due to ischemia caused by obliterating lesions of the small arterioles. These lesions are similar to those found in other localities in essential hypertension. The most common vascular changes are an increase in the thickness of the arteriolar wall and a decrease in the diameter of the lumen. The lesions are specific to hypertensive disease, with subendothelial hyalinosis in some cases, or thickening and an increased number of nuclei in the media in others.

The lesions may be initiated as the result of slight local trauma or even without it. Usually the first symptom is a painful red patch in the skin, which soon becomes blue and purpuric. Later, superficial necrosis develops, and finally ulceration appears which is often bilateral and symmetrical. The ulcer is located on the anterolateral aspect of the leg at the union of the lower and middle thirds (fig. 1). There may be an ulcer on one side and a simple pigmented spot on the other side. The ulcer becomes sensitive and painful; and the pain is not relieved by rest in bed. There is no history of thrombophlebitis, and there are no varicose veins. The dorsalis pedis arteries are palpable.

The diagnosis of hypertensive ulcer is made when ulceration such as is described above coincides with diastolic arterial hypertension in the arms and arterial hypertension in the legs, without clinical evidence of arterial occlusion or disturbance of the venous circulation.

Lumbar sympathectomy in the treatment of hypertensive ulcer is useful in properly selected patients.

Case Reports

Case 1. A woman, 59 years old, first seen in June 1954, had been known to have high blood pressure for at least five years. About one year after hypertension was diagnosed, an ulcer developed on her left leg. Six months before the consultation, another ulcer developed on the anterolateral aspect of the left leg. The latter ulcer was painful and resistant to medical treatment. Pain was not relieved by bed rest. The lesion started as a small, bluish-red flat spot in the skin. A hemorrhagic bleb developed soon and broke down into a superficial ulcer which gradually became larger and very painful.

Examination of the lower extremities revealed scars of the former ulcer on the right leg, and, on the left leg, an open ulcer on the anterolateral aspect

From the Vascular Clinic, Instituto Policlínico, Barcelona, Spain.

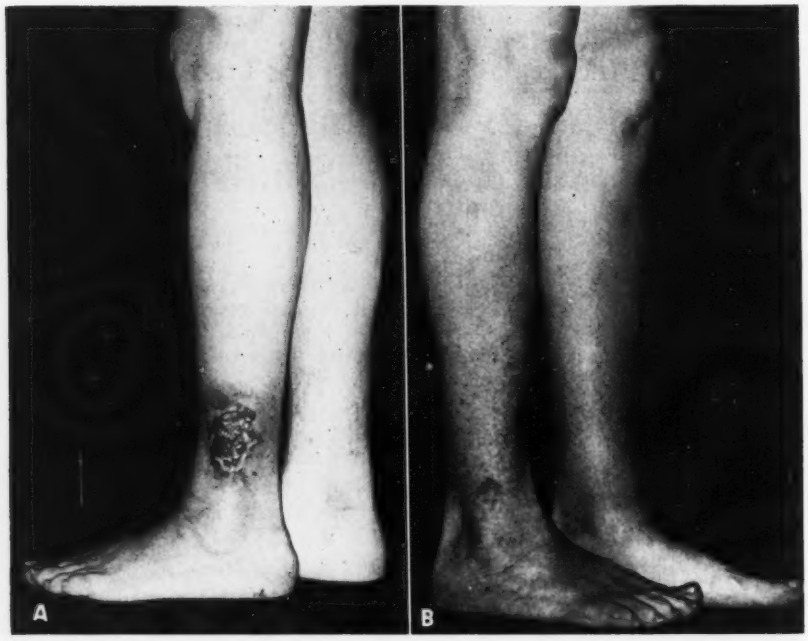

FIG. 1. Hypertensive ulcer of the lower extremities in a woman aged 59 years: A. Ulcer on the left lateral aspect. B. Symmetrical scar on the right lateral aspect.

at the union of the lower and middle thirds of the leg (fig. 1). The blood pressure was 270 mm. Hg systolic and 140 mm. Hg diastolic. The heart was enlarged. There was no evidence of varicose veins or of chronic venous insufficiency. Peripheral arterial pulsations were all normal.

On July 1, 1954, under general anesthesia, the second, third and fourth sympathetic lumbar ganglia on the left side were removed and a Tiersch graft made. On Aug. 16, 1954, the ulcer was completely healed.

Case 2. On April 23, 1948, a woman aged 58 years entered the hospital suffering from diastolic hypertension and a very painful ulcer on the right leg. The ulcer was superficial, not excavated, and with hardened edges. It occupied the anteroexterior aspect of the right leg at the union of the middle and lower third. No varices or arterial obliterations were detected. No edema was present. Below the knee oscillometry showed hypertension and hyperoscillometry. Arterial pressure in the arm 225/125; Marked aortic dilatation and hypertrophy of left ventricle were demonstrated radiologically.

On April 24, under general anesthesia, extirpation of the second, third and fourth sympathetic lumbar ganglia on the right side was done. On June 16, 1948, the ulcer was completely healed. On Sept. 29, 1948, the ulcer was still closed.

Later a similar and symmetrical ulcer developed on the other leg.

We are informed that later the patient had a cerebrovascular accident.

Case 3. On Dec. 2, 1946, a woman 55 years of age, came to the outpatient department. For six months she had had a painful ulcer on her left leg and troublesome paresthesia in both legs. She was very nervous and anxious and had attacks of spontaneous weeping. Three years before she had a similar ulcer on the right leg. Examination showed an ulcer on the outer side of the left leg, located at the union of the middle and lower third. It was surrounded by a pigmented zone which was also present symmetrically, on the other leg.

Very slight edema was present. No disturbance of venous circulation and no arterial occlusion were detected. There was hypertension and hyperoscillometry in the lower limbs. Arterial pressure in the arm was 195/120. Supplementary laboratory examinations revealed nothing abnormal.

The diagnosis was left hypertensive supramalleolar ulcer. The treatment was left lumbar sympathectomy which was performed on Dec. 31, 1946. Following this procedure the ulcer became painless and its appearance changed rapidly. Local thermometry at the level of the big toe showed a difference of 4 C. in favor of the operated side. Arterial pressure was lower. The patient's nervousness and emotional instability improved. A daily injection of splenic hormone was administered. Local treatment consisted of simple aseptic measures. She was

able to leave her bed in 12 days. The ulcer healed in 55 days.

Case 4. A woman 53 years of age, first seen in March 1953, had been known to have high blood pressure for at least 15 years. Hypertensive retinopathy with loss of vision in the left eye had preceded by six months a cerebrovascular accident. About four months before the consultation, a small, very painful, bluish flat spot developed on the skin of the right leg, and broke down into a superficial ulcer, which gradually became larger and very painful especially at night.

Examination showed two superficial ulcers a little proximal to the right lateral malleolus. Skiagram of the chest showed left ventricular enlargement and uncoiling of the aorta. Vision of the left eye had been lost. Hypertensive retinopathy, grade 3, was present on the other side. No varicose veins were present. The dorsalis pedis arteries were palpable.

Lumbar sympathectomy was performed on March 21, 1953. Later a Tiersch skin graft was made. The ulcer healed in two months and remained healed for 20 months.

Summary and Conclusions

The effects of lumbar sympathectomy in the treatment of hypertensive ulcer are presented.

Hypertensive ulcers are localized to the supramalleolar region, usually on the antero-lateral aspect at about the junction of the middle and lower thirds of the leg. Ulceration is often bilateral and symmetrical. The ulcers produce much pain which is not relieved by rest in bed. Varicose veins and chronic venous insufficiency are absent. Peripheral arterial pulsation are usually normal.

Four cases from the Vascular Clinic of the Instituto Policlínico are presented.

Summario in Interlingua

Es presentate un reporto del effectos de sympathectomia lumbar in le tractamento de ulceres hypertensive.

Ulceres hypertensive es localisate intra le region supramalleolar, usualmente al aspecto antero-lateral approximativemente al junction del secunde tertio con le tertio inferior del gamba. Le ulceration es frequentemente bilateral e symmetric. Le ulceres es dolorosissime e le patiente obtene nulle alleviamento per allectar se. Varices e chronic insufficientia venose es absente. Le pulsation arterial peripheric es usualmente normal.

Nos presenta 4 casos observate al Clinica Vascular del Instituto Polyclinic a Barcelona in Espania.

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Subacute Bacterial Endocarditis Arising in Mural Thrombi Following a Myocardial Infarction: A Case Report

By SEYMOUR JOFFE, M.D. AND HAROLD FEIL, M.D.

A case of subacute bacterial endocarditis arising in a thrombus covering myocardial infarction, with a necropsy, is reported. The patient died after an illness of four months duration. The clinical course was characterized by a low fever, congestive failure, petechiae, purpura, and ulceration of the skin. The rarity of this clinical picture is emphasized.

FEVER in a patient with heart disease frequently indicates infection or infarction of either the heart or lung. However, the occurrence of infection and infarction concomitantly in the heart is, at least statistically, extremely uncommon. Only four cases[1,2,3] have been reported in the literature of bacterial invasion of an acute myocardial infarction followed by abscess formation in the myocardium. Similarly, a purulent pericarditis following an acute infarction on the basis of coronary artery disease is extremely rare. In a series of 77 cases[4] of purulent pericarditis only one case of associated coronary thrombosis is recorded. In Bean's series[5] of 287 cases of myocardial infarction (all but five having coronary artery disease) 101 (32 per cent) had evidence of pericarditis and two of these (0.7 per cent) had a purulent process. These figures are in marked contrast to the high incidence of pulmonary infection as a terminal event in patients with coronary artery disease.

The case we are now presenting had a recent coronary artery occlusion with myocardial infarction. During convalescence he had jaundice, petechiae, purpura, and myocardial failure. This report is made because of the rarity of this clinical picture.

CASE REPORT

A 54 year old male was admitted to University Hospitals because of petechial eruption of five weeks duration. Eleven weeks prior to admission the patient had an acute myocardial infarction which was treated at home with bed rest, digitalis, and Aureomycin; the Aureomycin was given shortly after the episode of chest pain because of a suspected pneumonia. Convalescence was uneventful until nine weeks prior to admission when pretibial edema was noted. Diuretics (ammonium chloride and Mercuhydrin) were given with a fairly good response. He, however, reaccumulated edema fluid which became refractory to routine diuretic therapy. Six weeks prior to admission petechiae appeared in the lower limbs which progressed to areas of ulceration. Two weeks prior to admission the patient was hospitalized in another hospital where evidence was found of renal and hepatic dysfunction but no disturbance in the clotting mechanism. Laboratory data revealed the following: Hemoglobin 14 Gm. per 100 cc.; white blood cell count, 6500; 4 plus albuminuria with microscopic hematuria; blood urea nitrogen 53 mg. per 100 cc.; urea clearance, 40 per cent; cholesterol 86 mg. per 100 cc. and a bromsulphalein retention of 42 per cent. Bleeding time, clotting time, clot retraction and platelet count were all normal.

When seen at University Hospitals the patient appeared acutely and chronically ill. The blood pressure was 112/100, pulse, 82 and regular in rhythm, respirations 24 per minute and temperature 37.2 C. The sclerae were icteric and there was moderately intense jaundice. There were numerous petechial and purpuric areas over the legs and arms. On the posterior aspects of both legs these areas had become ulcerated. Petechiae were also present in the buccal mucosa. The lungs were clear to auscultation and percussion. The heart was enlarged to 1 fingerbreadth beyond the midclavicular line. The heart sounds were distant. The liver extended 3 fingerbreadths below the right costal margin and the edge of the spleen was palpated on inspiration. There was 3 plus pretibial and 1 plus presacral edema. Neurological examination revealed no abnormalities.

From the Department of Medicine, Western Reserve University and the University Hospitals of Cleveland, Cleveland, O.

Laboratory data found on admission were as follows: Hemoglobin 16.8 Gm. per 100 cc.; red blood cell count 5.95 million; hematocrit 65 per cent; white blood cell count 11,050, with a normal differential; platelets 252,950; bleeding time 2 min. 40 sec.; clotting time 5 minutes; clot retraction beginning in 3 hours; prothrombin time 25.5 seconds (control 34 seconds); thrombin time 34 seconds (control 30 seconds)*. Examination of the urine showed a specific gravity of 1.012, 2 plus albumin 50 to 60 red blood cells, and 5 to 8 white blood cells, per high power field. Total serum protein was 7 Gm., albumin 3.6 Gm., globulin 3.4 Gm.; blood urea nitrogen 30 mg. per 100 cc. The icteric index was 36; cephalin flocculation 1 plus; thymol turbidity 0.2 units; total bilirubin 7.3 mg., indirect 2.6, direct 4.7; alkaline phosphatase 8.3 units; urine urobilinogen 0.8 Ehrlich units. Sodium ranged from 120 to 128 mEq., potassium from 5.6 to 6.1 mEq., and chloride from 92 to 98 mEq per liter. Kline exclusion test was negative. Stool was positive for occult blood on three occasions. Rumpel-Leede's test was weakly positive. No bromide or barbiturate was detected in blood. The electrocardiogram showed first degree A-V block, incomplete right bundle branch block and evidence of anterior wall myocardial infarction. Culture of petechiae showed no growth, and biopsy demonstrated focal acute inflammation in skeletal muscle and subcutaneous tissue. The venous pressure was 285 mm. of saline.

On admission drug toxicity was suspected. With this in mind, drugs were given to the patient with extreme caution. Mercurials were avoided for this reason and the congestive failure increased. New showers of petechiae developed, the jaundice deepened, and bilateral pleural effusions appeared. Thoracenteses were performed on four occasions. The pleural fluid had a specific gravity ranging from 1.012 to 1.016. Large numbers of white cells (8050 to 54,900) with a preponderance of polys were found. *Streptococcus viridans*, *Staphylococcus aureus* and *Aerobacter aerogenes* were found. Cell blocks of the fluid were all negative for tumor cells. Bone marrow showed leukophagocytosis as sometimes seen in subacute bacterial endocarditis. Culture of the bone marrow revealed no growth. Six blood cultures showed no growth in seven days. A urine culture (yielded *Proteus vulgaris* and *Streptococcus viridans*. The patient had a low grade fever, never going above 38.2 C. His clinical condition progressively deteriorated, being marked by episodes of lethargy and confusion. On the day prior to death the patient was given test doses of penicillin and Mercuhydrin without ill effect, before planned therapy.

Postmortem examination.† The skin was jaundiced. There were numerous petechiae and purpuric spots with ulcers of the skin of the arms and legs. A muscle biopsy showed myositis (fig. 1). The heart weighed 600 Gm. with hypertrophy of both ventricles, the left ventricular wall measuring 1.5 cm. and the right ventricle measuring 0.6 cm. in thickness. The pericardial surfaces were fibrous and shaggy. There was old thrombotic occlusion of the left descending coronary artery (fig. 2) with resultant infarction of the anterior two-thirds of the interventricular septum, the anterior wall and apex of the left ventricle. The myocardium in these areas was completely replaced by firm, white, fibrous tissue. The left ventricle was moderately dilated and over the anterior wall of the apex the wall bulged outwards. There was a mural thrombus covering the anterior half of the interventricular septum and all of the anterior wall of the left ventricle, and extending from 2 cm. below the aortic valve to the apex (fig. 3). It was covered over by a smooth, pale-gray layer of endothelium and centrally consisted of friable reddish-brown material. Immediately adjacent to the opening of the coronary sinus the endocardium of the right atrium was covered by a firm, dark, reddish-brown thrombus (fig. 4). On microscopic section the myocardium of the left atrium and a very small portion of the right atrium was the site of a subendocardial infarction. In the thrombi covering the infarcted region of the left ventricle (fig. 5) and right atrium,

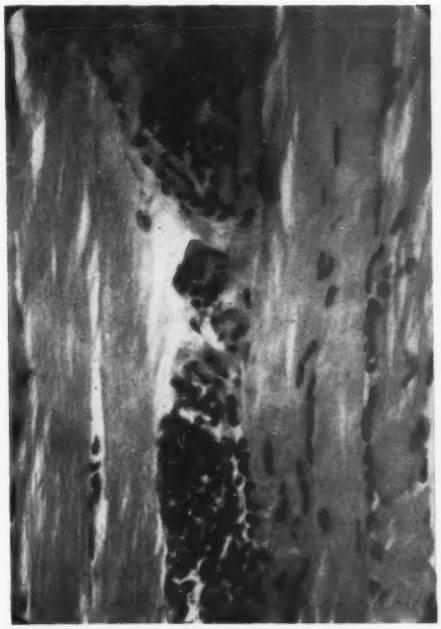

FIG. 1. Section of gastrocnemius muscle showing acute focal myositis.

* The prothrombin and thrombin times were kindly done by Dr. Oscar Ratnoff to whom we are indebted.

† We are indebted to Dr. Simon Koletsky for review of the pathological material and its interpretation.

FIG. 2. Recanalized thrombus in the anterior descending ramus of the left coronary artery.

FIG. 3. Showing mural thrombus in left ventricle adjacent to myocardial infarction.

FIG. 4. Mural thrombus in right atrium adjacent to atrial infarction.

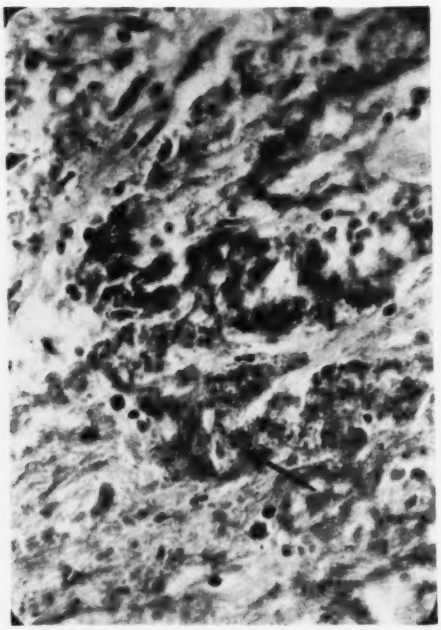

FIG. 5. Section of left ventricle showing mural thrombus with bacterial invasion. Arrow points to areas with bacterial invasion, identified under higher magnification.

bacterial invasion was demonstrated on histological examination. This consisted of clumps and clusters of Gram positive cocci which were unfortunately not cultured because infection was not suspected on gross examination. The aortic valve showed subcommissural adhesions between the right and left anterior cusps. Each cusp was shortened with a thickened firm nodular margin which was probably the result of old rheumatic valvulitis. There were no vegetations.

The pleural spaces showed bilateral serous effusions (600 cc. each), and extensive pleural adhesions, many of which enclosed small pockets of purulent material. There were organizing abscesses in the right upper, right lower, and left lower lobes of the lungs with focal organizing pneumonia, pulmonary hemorrhage and necrosis. In the left lower lobe abscess *Aerobacter aerogenes*, *Alkaligenes fecalis*, and *Staphylococcus aureus*, (coagulase negative) were recovered. There were bilateral pulmonary infarcts with an organizing thrombus occluding the pulmonary artery to the right upper lobe (fig. 6). Microscopic section of this thrombus showed the presence of bacteria.

The esophagus was the site of an acute inflammation. The kidneys showed tubular bile casts and tubular degeneration. There was generalized hyperemia of the viscera and the remainder of the necropsy was not remarkable.

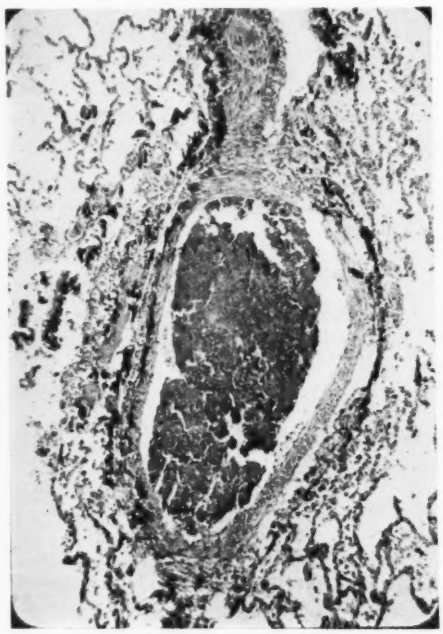

FIG. 6. Section of pulmonary artery with thrombus

DISCUSSION

The patient died four months after myocardial infarction with a final illness characterized by congestive failure, petechiae, purpura, ulceration of the skin, and subsequently, by hematuria, jaundice, evidence of septic pulmonary infarcts and inflammatory pleural effusions. Bacteria were demonstrated in sections from mural thrombi of the left ventricle and the right atrium. We believe that infection of mural thrombi associated with myocardial infarction took place. Peripheral and pulmonary emboli resulted. The original source of infection was never demonstrated. All blood cultures were negative, as found in a small percentage of cases of subacute bacterial endocarditis.

Subacute bacterial endocarditis classically arises on a valve deformed by rheumatic heart disease, on congenital lesions, or rarely on calcareous or syphilitic valvular lesions. The mural endocardium may become secondarily involved by direct contact or extension. In this patient, while the mural endocardium was involved, the valves remained free of infection. This is extremely uncommon in either acute or subacute bacterial endocarditis. Schulz[6] has reported a case of puerperal sepsis with a circumscribed area of mural endocardium of the left ventricle, covered with fibrin and soft thrombi while the valvular endocardium was not involved. This may also occasionally occur in pneumococcal endocarditis. Morrison[7] cited one case of subacute bacterial endocarditis, arising only on the mural endocardium. Endocarditis occurring subsequent to a coronary occlusion is not unheard of. Libman and Friedberg[8] reported a patient who had suffered two attacks of coronary occlusion and in whom subacute bacterial endocarditis occurred on the basis of an old aortic insufficiency. Lemann[9] has reported a case in which the infection developed on a mitral valve which had been made insufficient because of infarction of the left posterior papillary muscle due to a coronary artery thrombosis. Libman and Friedberg[8] noted two other cases in the literature in which a similar mechanism was involved. The unusual feature in our case is that

mural thrombi occurring secondary to myocardial infarction predisposed to subacute bacterial endocarditis. The aortic valve was the site of a healed rheumatic endocarditis and was not involved in the process.

Summary

A case report is presented of a patient with recent myocardial infarction with mural thrombi which became infected and led to peripheral and pulmonary embolization. The low incidence of the concomitant occurrence of cardiac infection and myocardial infarction is discussed.

Summario in Interlingua

Es reportate un caso de recente infarcimento myocardiac con thrombos parietal que deveniva inficite e causava embolisation peripheric e pulmonar. Es discutite le infrequentia del co-occurrentia de infection cardiac e infarcimento myocardiac.

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Angiocardiographic Demonstration of Occlusive Auricular Thrombi in Dogs

By JOHN L. READ, M.D., LEWIS H. BOSHER, M.D., FELIX FERRARU, M.D., SAMUEL RICHMAN, M.D. AND RENO R. PORTER, M.D.

Simulated occlusive auricular thrombi were produced in six dogs by surgically invaginating the left auricular appendage. Angiocardiographic studies were performed in five of the dogs and in each case revealed these thrombi as clear cut filling defects. The significance and clinical application of these observations is discussed.

IN a previous paper[1] it was postulated that in view of the encouraging progress made in both the diagnosis and surgical alleviation of a variety of cardiovascular lesions, it might be hoped that ultimately such thrombi could be demonstrated by angiocardiographic technique and subsequently removed in conjunction with a mitral valvotomy. Since such thrombi have invariably terminated fatally, early and accurate diagnosis could conceivably represent a life saving measure.

The incidence of occlusive auricular thrombi has been variously reported to range from 1 in 3000[2] to 1 in 540[3] autopsies. The incidence of such thrombi in patients with rheumatic heart disease has been reported as 1 in 52 cases by Garvin[4] and 1 in 32 cases by Wallach and coworkers.[3] Evans and Benson[5] found an incidence of one out of eight patients coming to autopsy with mitral stenosis.

The value of angiocardiography in detecting a similar object within the heart has already been demonstrated in man by Bahnson and Newman.[6] They presented the case of a large pedunculated myxoma, which was demonstrated as a large filling defect in the right auricle following injection of Diodrast through a number 8 catheter. The tumor was successfully removed but the patient succumbed 24 days later of postoperative complications. As a result of our experience with four case of occlusive auricular thrombi, we decided to study the diagnostic efficacy of angiocardiography in dogs following the insertion of an artificial thrombus into the left auricle.

FIG. 1. The heart from dog 1 is shown viewed from apex to base with the lower two thirds of both ventricles removed. The invaginated left auricular appendage, T, can be seen protruding into the left auricular cavity, LA. RV, right ventricle; IVS, intraventricular septum; LV, left ventricle; MV, mitral valve; AV, aortic valve.

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This study was made possible by a grant from the Department of Research and Education, Veterans Administration, Washington, D. C.

Material and Methods

Six dogs, ranging in weight from 25 to 35 kg., were selected for this study. Using aseptic technique, the left auricular appendage was inverted and tightly ligated so as to simulate a pedunculated thrombus of the left auricle. The first dog was sacrificed immediately following this operation in order to examine the appearance of the simulated thrombus (see fig. 1). At least one angiocardiographic study was performed in each of the five remaining dogs following inversion of the left auricular appendage. One of the dogs had, in addition, a ligature passed around the base of the mitral valve according to the technic of Ellison and associates.[7] Thus, it was possible to gradually narrow this orifice, and to produce varying degrees of mitral stenosis and simultaneously to record pressures within various segments of the vascular tree.

For the angiocardiographic studies, the dogs were placed in the left lateral decubitus position with the thorax resting on the cassette of a Fairchild roentgen camera. The camera was adjusted so that frames were automatically changed every half second.

Twenty c.c. of a 60 per cent Diodrast solution were injected rapidly through the tip of a number 8 cardiac catheter or through a needle in the jugular vein. Figure 2 demonstrates the serial findings observed in one dog. In this dog, the anterior and

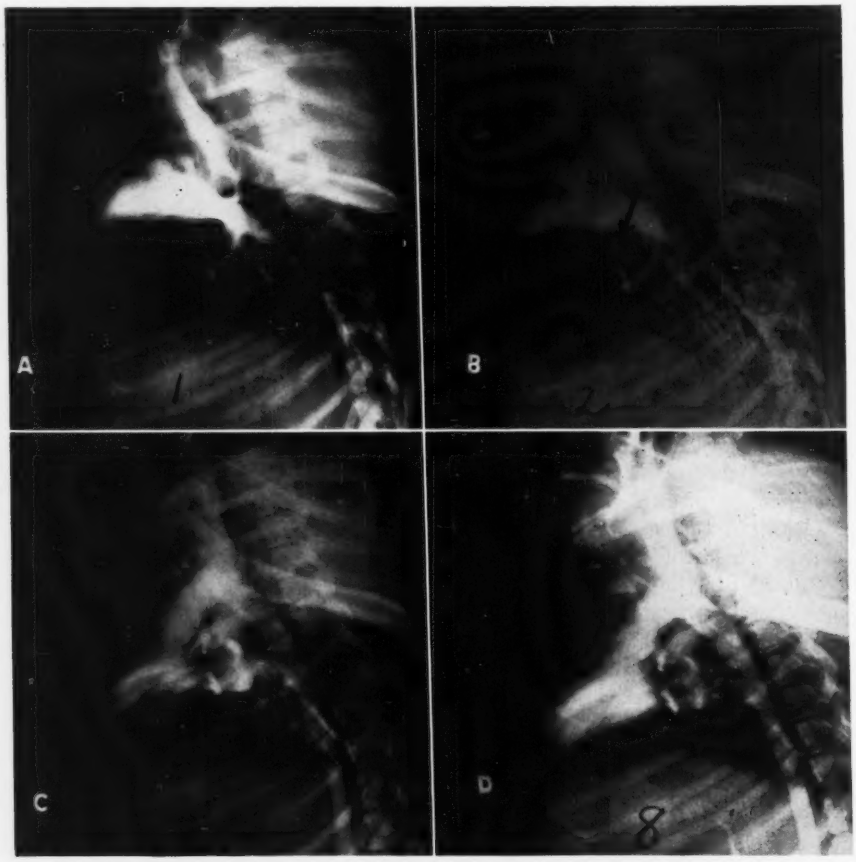

Fig. 2. (A) After one second the contrast material fills the superior vena cava, right auricle, right ventricle, and pulmonary vessels. (B) After one and one-half seconds, the contrast material has been distributed throughout the pulmonary vascular bed. Arrows indicate radiopaque material used to localize the point of invagination of the auricular appendage. (C) After three seconds, the contrast material fills the left auricle, left ventricle and aorta. A filling defect can be distinctly visualized in the left auricle. (D) After four and one-half seconds, the contrast material is beginning to fade from the left auricle but still outlines a filling defect.

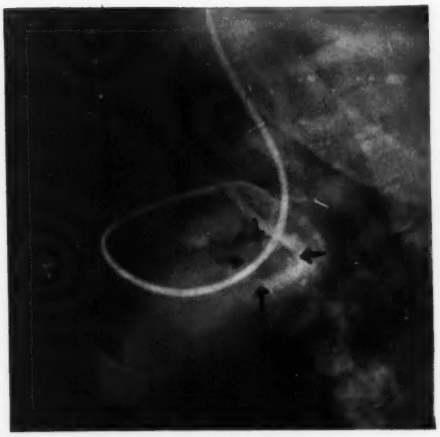

FIG. 3. Angiocardiogram after four seconds in dog 2. The Diodrast could not be injected as rapidly through the catheter so that the radiopaque material does not give as sharp a contrast as is seen in figure 2. The arrows mark the boundaries of the filling defect seen in the left auricle.

posterior boundaries of the auricular appendage have been marked by strips of radiopaque gauze in order to show that the filling defect observed actually appeared in this position. Figure 3 is an angiocardiogram in another dog. The Diodrast in this case was injected through the tip of a number 8 catheter placed in the pulmonary artery. The radiopaque material could not be injected as rapidly through the catheter as it could through a large needle in the jugular vein and, therefore, the contrast was not so marked as shown in figure 1 where Diodrast was injected through an intrajugular needle.

DISCUSSION

It has been shown that occlusive thrombi of the left auricle can be demonstrated consistently as clear-cut filling defects by angiocardiography. Since occlusive thrombi of the left auricle have been found in approximately 1 out of every 8 autopsied cases of mitral stenosis[5] and 1 out of every 10 cases in our series, the use of angiocardiography may be of considerable value in demonstrating such thrombi in human subjects whose clinical picture might suggest this condition. The growing popularity of angiocardiography in the selection of patients for mitral surgery[8] makes it highly probable that such a thrombus will ultimately be both demonstrated as a filling defect by Diodrast injection and successfully removed through an auricular incision. Further studies relating to the hemodynamics in patients with occlusive thrombi of the auricles are in progress in an attempt to better delineate the clinical syndrome.

SUMMARY

Simulated occlusive thrombi of the left auricle were created surgically in six dogs by invaginating the left auricular appendage. Angiocardiographic studies were performed in five of the dogs. In each case, the thrombus was demonstrated as a clear cut filling defect. The significance of this procedure and its human application is discussed.

SUMMARIO IN INTERLINGUA

Thrombos occlusive del auriculo sinistre esseva simulate chirurgicamente in sex canes per invagination del sinistre annexo auricular. In cinque casos studios angiocardiographic esseva executate. In omne casos le thrombo se manifestava clarmente per un defecto de replenamento. Es discutite le signification de nostre technica e su application a humanos.

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Occlusive Auricular Thrombi

By JOHN L. READ, M.D., RENO R. PORTER, M.D., SIMON RUSSI, M.D. AND JOSEPH R. KRIZ, M.D.

The literature on occlusive thrombi of the auricles has been reviewed in order to identify the symptom complex attributed to this condition. The clinicopathological findings are presented in four new cases which fit this symptom complex. Two cases are notable in that one is that of a ball thrombus occurring in the absence of mitral stenosis and another the first reported case of pedunculated thrombus of the right auricle.

ONE of the most interesting syndromes encountered in clinical medicine is that which develops subsequent to an occluding thrombus of the auricle. This is particularly true in the extremely rare case which involves the right auricle. The term "ball thrombus" was introduced by Wood,[1] who reported the first case in 1814. In his now classic monograph published in 1924, Abramson[2] made a complete survey of the literature. He reviewed 20 cases of ball thrombus of the heart and added one of his own. The first accepted case of occluding thrombus of the right auricle was reported by Wright and his coworkers[3] in 1944.

Von Ziemssen[4], in 1890, originally suggested the clinical criteria for suspecting the diagnosis of ball-valve thrombus. In view of almost identical signs and symptoms occurring in his three reported cases, he suggested that the diagnosis of ball and pedunculated thrombi in the left auricle could be made in the presence of the following findings: (1) the presence of severe mitral stenosis associated with symptoms of extreme obstruction to the blood stream of the left heart, and (2) edema, coldness, and gangrene of the feet. He attributed the gangrene to thrombosis following extreme diminution in peripheral blood flow, less often to embolism. According to Abramson,[2] most writers of that day looked upon the syndrome as a chance occurrence and, if not, one certainly compatible with a high grade of mitral stenosis and the endocarditis which so often accompanies it. Bozzolo,[5] however, in 1896, focused attention upon Von Ziemssen's[4] criteria with a case diagnosed during life and elaborated upon Von Ziemssen's clinical data. The former felt that the outstanding features of thrombosis of the left auricle were (1) signs of mitral stenosis, (2) signs of grave obstruction of the circulation to the left heart such as cyanosis, dyspnea, and cold extremities, (3) extreme feebleness of the peripheral pulses, and (4) the presence of many areas of gangrene in the lower extremities. The importance of the latter finding was reiterated by Redtenbacher,[6] who stated that patients who lived long enough with cardiac thrombosis would inevitably develop gangrene of the extremities. Abramson emphasized the frequency of hemiplegia.

The popular sentiment at the turn of the century was that there was little in either the history or physical examination which might permit one to state that intracardiac thrombosis existed in a given patient with mitral stenosis. In 1909, Smithies[7] appraised the clinical picture with the following observation: "It would seem to me, therefore, that the antemortem diagnosis of certain heart thrombi is not altogether impossible if the physical signs are carefully observed and recorded, and of these physical signs, I would lay especial stress on atypical peripheral vascular manifestations with more or less characteristic auscultatory and percussion signs in the heart itself. The manifestation of the embolic process should always furnish significant information."

Although the symtom complex produced by massive auricular thrombosis is identical with that subsequent to a pedunculated or ball

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thrombus, the interest of most medical authors has centered almost exclusively about the select group designated "ball thrombi." These must fulfill certain rigid criteria as defined by Welch;[8] namely, there must be (1) entire absence of attachment with consequent free motility, (2) imprisonment in consequence of an excess in the diameter of the first narrowing in the circulatory passage ahead of it, and (3) such consistency and shape that the thrombus will not of necessity lodge as an embolus in passage. Obviously, as Aronstein and Neuman[9] have observed, such a separation is exclusive but of academic interest since, clinically similar symptoms may be produced by a pedunculated thrombus and, as Yuskis[10] and the authors have discovered, by a diffuse auricular thrombus. Of the 21 cases reported by Abramson, only two had been diagnosed during life.

Of the cases reviewed, 12 were females and 4 were males. The sex was not reported in five cases. The age was over 30 years in 12 cases with the most frequent decade being the fifth. In every case there was mitral stenosis of a marked degree. Since Abramson's report, this diagnosis has been made with increasing frequency during life. The incidence of ball thrombi derived from several large series[11-13] is roughly 1 in 2000 necropsies.

In 1934, Elson[14] made one of the most significant contributions to the clinical diagnosis of ball thrombi. "The most important diagnostic feature, in our opinion, is the presence of comparatively rapid and transitory changes in the peripheral circulation, such as marked cyanosis or even gangrene which may involve the finger tips, toes, or tip of the nose. Cadaveric coldness, may occur suddenly, and quickly improve or disappear. The disappearance or diminution of pulsations, not from one extremity, but from several of them including both upper and lower, and their relatively rapid restoration should be emphasized. Such symptoms cannot be explained on the basis of peripheral emboli alone."

In 1948, Evans and Benson[15] attempted to evaluate the effects of the mass itself. Symptoms ascribed to 46 cases of ball thrombi reported up to that time were compared with those arising in 27 tumors of the left auricle. They found no significant difference in symptomatology. However, in 46 patients with mitral stenosis, who came to necropsy in the London hospital, only one patient who manifested chest pain as a significant feature during life failed to demonstrate an occlusive thrombus of the left auricle. Six of the 46 patients demonstrated occlusive thrombi. They therefore stress the importance of cardiac pain indistinguishable from that following coronary insufficiency. Unfortunately, four of their six patients with occlusive thrombi had no complaints of such pain during life.

A review of the available literature to date reveals approximately 60 reported cases of ball thrombi of the auricles and many more cases of massive and pedunculated thrombi.

Case Reports

During a six-month period in 1952, we were unusually fortunate at the McGuire Veterans Administration Hospital in seeing four cases of occlusive auricular thrombi, which we have considered to be especially significant from the clinical standpoint. The first case is rare in that it represents one of the few reported instances of ball thrombus of the left auricle occurring in the absence of mitral stenosis. The second case, and only one with rheumatic heart disease, is that of a massive thrombus lining almost the entire left auricle. The third is a case of triple thrombi of the left auricle attached loosely to the auricular wall in such a manner as to almost completely obliterate the auricular lumen. The fourth case is to our current knowledge, the first reported case of a pedunculated thrombus of the right auricle. Only two authenticated cases of ball thrombi of the right auricle have been reported to date.[3, 16]

Case 1. P. M., a 62 year-old Negro male, was admitted to the Surgical Service on Feb. 23, 1952, in a comatose state with gangrene of the right leg and evidence of peripheral vascular collapse. Subsequent history revealed a 40-pound weight loss and irregular heart action beginning two weeks previously followed by sudden pain in his right leg. He also noted recurring, intermittent abdominal cramps every few minutes of progressively increasing severity beginning 24 hours before. There

was persistent nausea, vomiting and passage of stools mixed with fresh blood. Past history revealed a history of hypertension of 12 years' duration, chronic alcoholism, and repeated urinary tract obstruction due to urethral stricture. There were four previous admissions for treatment of cardiac decompensation and urethral stricture. During these admissions he complained of dyspnea and epigastric pain and distension. His response to digitalis had always been adequate.

Physical examination at this time revealed a semicomatose Negro man in a state of considerable dehydration and inanition. He failed to respond to stimuli except to stir restlessly. The temperature was 96 F., respirations 22, pulse 150 beats per minute and blood pressure 100/80. The thorax was moderately emphysematous. The lungs were clear except for coarse breath sounds which were somewhat suppressed at the left base. The cardiac borders could not be defined satisfactorily by percussion. Heart sounds were heard best in the sixth left intercostal space along the sternum. The rhythm was rapid and grossly irregular. There were no definite murmurs; however, a distant whistling, rumbling sound was audible at the apex. This was felt to be probably of respiratory origin, but possibly represented an early mitral systolic or presystolic murmur. Examination of the extremities revealed bilateral femoral pulsations. The right lower leg was cold and revealed changes of early gangrene involving the right foot. There was a blotchy discoloration which extended to a point just below the knee where it coincided with the line of temperature demarcation. The right popliteal artery could not be palpated. There was 1 plus pitting edema present bilaterally. An electrocardiogram revealed auricular fibrillation with a rapid ventricular response (150) and long runs of ventricular tachycardia. He was given 1350 mg. of Pronestyl intravenously during the next six hours with complete disappearance of ventricular tachycardia and extra systoles. He was digitalized during the next 16 hours with 2 mg. of Cedilanid intravenously and intramuscular Digiglusin. His ventricular rate dropped to 90 beats per minute and he gradually regained consciousness on the afternoon of February 24.

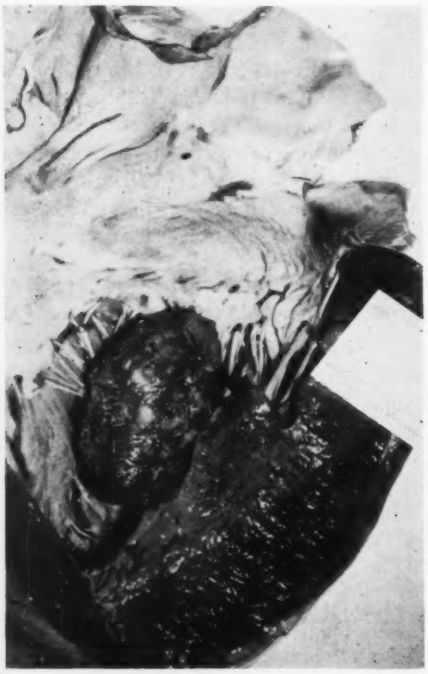

FIG. 1. An egg-shaped ball thrombus measuring 5.0 by 3.5 cm. is seen lying within the chordae tendinae of the mitral valve. It is free of any attachments and has dropped from the left auricle during the process of cutting the heart. Note the marked left ventricular hypertrophy.

Physical examination at this time, the day after admission, revealed exquisite tenderness and spasm of both upper abdominal quadrants. Examination of the heart and lungs was unchanged except that the previously described whistling sound could no longer be heard. That evening he again lapsed into coma. This was accompanied by increasing abdominal distension, vomiting, passage of tarry stools, fever and the appearance of an uremic frost on February 25. During this time the previously described murmur or respiratory sound again became audible. The night nurse noted that his pulse could often not be obtained at the wrist until the patient was turned on his side when it would come through quite well. He progressed rapidly into a uremic state and expired on Feb. 26, 1953.

Postmortem Examination: The heart weighed 900 Gm. There was a moderate dilatation, particularly of the auricles. Both ventricles were hypertrophied, the left ventricle measuring 2.5 cm. in thickness and the right 0.8 cm. An egg-shaped ball thrombus measuring approximately 5.0 by 3.5 cm. was found lying free within the left auricle (see fig. 1). The center was necrotic and yielded a pink-brown opaque fluid on puncture. All valves were normal. The coronary arteries were large and demonstrated no arteriosclerosis. The lungs were emphysematous and presented no other abnormalities.

Other pathologic findings included: an old myocardial infarction; thrombosis of the left popliteal artery with gangrene of the right lower leg; thrombosis of the coeliac artery; infarcts of the spleen, kidney and testicles; encephalomalacia; chronic hepatitis and a periurethral abscess.

Case 2. C. G., a 37 year-old white man, entered the hospital 48 hours after the sudden onset of severe

pain in his right chest, which was aggravated by respiration and accompanied by repeated bouts of hemoptysis. He was first seen at another hospital where physical examination demonstrated a pleural friction rub and a precordial thrill. The heart beat was rapid and grossly irregular. His temperature was 103 F. and there was a moderate leukocytosis. He had been started on penicillin and chloramphenicol therapy.

Chest roentgenogram revealed a greatly enlarged heart and a density in the left lung field which was interpreted as representing a pulmonary infarct. He gave a past history of rheumatic fever at age 14 and had apparently enjoyed good health until six months previously when he had been treated for a right middle lobe pneumonia and "heart trouble".

On admission, he presented a picture of collapse accompanied by mental confusion and marked dyspnea. He was moderately cyanotic about the face, lips and tips of his fingers and toes. His veins were collapsed. He complained of pain in his right side and repeatedly expectorated bright red blood. Examination of the chest revealed marked splinting, particularly on the right. There was dullness to percussion with medium moist rales elicited over both bases. No friction rub could be demonstrated. The heart was greatly enlarged. The rhythm was grossly irregular with a rapid rate and a considerable pulse deficit. There was a precordial thrill and a questionable pericardial friction rub. There were no definite cardiac murmurs. Blood pressure was 80/60. Examination of the abdomen revealed liver dullness extending 2 to 3 cm. below the right costal margin. An electrocardiogram revealed auricular fibrillation with a ventricular response of 150, runs of ventricular tachycardia, and right ventricular strain.

The patient was treated with nasal oxygen, intravenous digitalization and Levophed in an attempt to combat his vascular collapse. He improved somewhat during the next six hours, but thereafter enacted an unusual and dramatic sequence of events. His clinical course was punctuated by repetitive episodes during which he would suddenly lapse into a state of profound collapse during which neither blood pressure nor pulse could be obtained. His attacks were invariably preceded by a period of irrational behavior, intense cyanosis about the face and lips, and inability to talk. This state was followed almost immediately by a generalized seizure lasting two or three minutes. Thereafter, a very rapid, irregular pulse gradually became apparent and the blood pressure once more could be obtained, although it never exceeded about 70/50 despite Levophed. His recovery became poorer and poorer following each seizure. After his fourth attack he failed to revive and expired 22 hours after admission.

The clinical diagnoses were: (1) Rheumatic heart disease with myocarditis, mitral stenosis and occlusive thrombus of the left auricle, and (2) pulmonary infarction.

FIG. 2. The left heart is exposed and reveals a diffuse, adherent thrombus, which actually lines about two thirds of the left auricular wall. The mitral valve is considerably scarred.

Postmortem Examination: The heart weighed 850 Gm. and seemed to be unusually flabby. The left auricle and right ventricle were greatly dilated. There was slight dilatation of the left ventricle. The right ventricle was hypertrophied and measured 1 cm. in thickness. The left measured 1.5 cm. The left auricle was almost obliterated by a diffuse mural thrombus which varied in thickness from 0.5 to 1.3 cm. and lined almost the entire left auricular wall (see fig. 2). The mitral valve was stenotic and of a button-hole configuration. The remaining valves appeared normal. The coronary arteries were normal.

Microscopic examination was consistent with rheumatic myocarditis.

Other pathologic findings included: Edema and congestion of the lungs; infarction of the left lower lobe of the lung; chronic passive congestion of the liver and spleen, and pleural adhesions on the right.

Case 3. R. B., a 60 year-old, white man was admitted to the hospital on July 13, 1952, with a tentative diagnosis of acute coronary occlusion. A history was difficult to obtain because of profound

deafness and impaired cerebration; however, the pertinent facts were obtained in a letter from his family physician and from interviews with his wife. He had been treated during the previous 16 days for an arterial occlusion of his right lower leg, which had responded to conservative therapy. On the morning of admission, he suddenly developed crushing substernal pain followed immediately by deep cyanosis and unconsciousness. He gave a past history of three similar attacks during the previous year. Two of these had been associated with transient hemiplegia, which had resulted in some cumulative weakness. He had been completely disabled by his attacks since December 1951. At times, his seizures were preceded by a sharp, stabbing, epigastric pain. He had experienced an attack similar to the one seen on admission while enroute to the hospital.

Physical examination on admission revealed an elderly and markedly dyspneic man. His face and upper thorax presented a dusky, cyanotic hue. The retinal arterioles were the site of moderate arteriosclerosis. The chest appeared markedly emphysematous. Auscultation elicited many rhonchi and wheezes with moist basilar rales bilaterally. The heart was moderately enlarged to percussion. Heart sounds were quite distant with a sinus tachycardia (110 per minute). There were no definite murmurs or thrills. Blood pressure was 110/70. The abdomen was moderately distended and the liver edge was palpable 3 to 4 cm. below the right costal margin and moderately tender. Examination of the legs revealed a 2 plus edema of the right leg with impaired pulsations, some pallor and coolness as compared with the left.

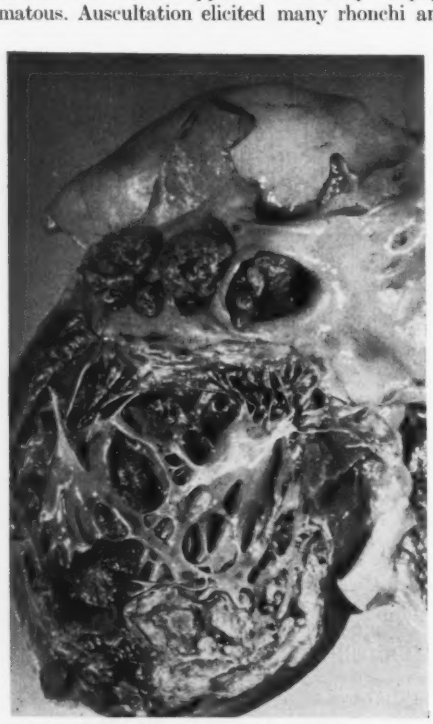

FIG. 3. The left auricle and ventricle are seen to be considerably dilated. Numerous, almost confluent, mural thrombi, cover the left ventricle. The left auricle contains three roughly rounded mural or pedunculated thrombi, which meet in the intact auricle so as to practically occlude that chamber.

Laboratory Data: Hemoglobin was 11.3 Gm., sedimentation rate 32 mm. in 1 hour, hematocrit 41, and white blood cells 11,350 per cubic millimeter with 81 per cent polymorphonuclear leukocytes. Urine contained 1 plus albumin. Wassermann test was positive. Blood urea nitrogen was 33 mg., and fasting blood sugar 87 mg. per 100 cc. Roentgenogram of the chest demonstrated a moderately enlarged heart with areas of possible pneumonitis in the left upper lung field. The electrocardiogram revealed sinus tachycardia (rate 110), low voltage, and abnormal T waves.

A tentative diagnosis was made of arteriosclerotic heart disease and superimposed pulmonary disease with syncopal attacks on the basis of a Stokes-Adam's syndrome or occlusive auricular thrombosis. The patient required frequent aminophyllin and morphine.

He remained relatively comfortable until midnight on July 14, 1952, when he experienced a sudden smothering sensation accompanied by intense cyanosis, profuse icy perspiration and lapsed into a semicomatose state. During this period, neither pulse nor blood pressure could be obtained. Auscultation revealed marked pulmonary congestion. He was given intravenous morphine and Cedilanid with gradual improvement. On July 16, 1952, he was again seized with a smothering sensation. His pulse rate was 140 and very rapid and weak. The systolic pressure was 60 mm. Hg, the diastolic could not be obtained. Gross pulmonary edema developed. He appeared quite cyanotic and had marked distension of his neck veins.

On July 18, 1952, he began to cough up bright red blood. He continued to have almost daily paroxysms. On July 30, 1952, he suddenly grimaced as though in extreme pain, clutched his chest, became extremely cyanotic, gasped for breath and expired.

Postmortem Findings: The heart weighed 600 Gm. The left ventricle was slightly dilated with marked thinning and scarring. There was a large yellow area of necrosis with softening involving the entire posterior wall of the left ventricle. There were numerous almost confluent mural thrombi in both ventricles. The left auricle contained three rounded mural or pedunculated thrombi which met so as to practically occlude that chamber (see fig. 3). The

coronary arteries revealed marked atherosclerosis. The left ventricle varied in thickness from 0.7 to 1.5 cm.

Other pathologic findings include infarction of left lung, right pleural adhesions, fibrinous pleuritis on the left, generalized arteriosclerosis, and syphilitic aortitis.

Case 4. T. G., a 45 year-old white male, entered the hospital with a history of intermittent claudication in his legs of eight years duration. Six years previously he was told by a physician that no blood pressure could be obtained in his right arm, a condition which persisted for the remainder of his life. One year later he developed a transient left sided hemiplegia with residual fleeting paresthesias in all extremities and more frequent leg cramps after exertion. In May 1951, he was hospitalized for one month during which time he received anticoagulant therapy for a myocardial infarction. In September 1951, he noted the onset of daily fever, chills, and sweats. Because of these symptoms, he entered a University Hospital where he was found to have a positive tuberculin skin test and what appeared to be tuberculous giant cells in his sternal marrow. His symptoms were alleviated by streptomycin therapy and he was discharged with a tentative diagnosis of miliary tuberculosis or hidden carcinoma. During the week preceding this admission he developed generalized ecchymosis with severe joint pains, particularly in his left hand. This member became cyanotic and the terminal phalanx of his left ring finger became gangrenous.

Physical examination on admission revealed a poorly nourished, chronically ill, white man. The temperature was 101 F. Pertinent findings were limited to the cardiovascular system, skin and extremities. The heart was of normal size and configuration. The rate was 110 beats per minute with a regular rhythm. There was a grade 2 apical systolic murmur. The blood pressure was 122/90 in the left arm, 140/78 in both legs, but could not be obtained in the right arm. Femoral and pedal pulsations were adequate. The abdomen was moderately distended with gas and the liver edge was palpated 3 fingerbreadths below the right costal margin. It was soft and moderately tender. The tips of all fingers of the left hand were cyanotic and tender. The tip of the little finger was black and dry. Examination of the skin revealed splotchy, brownish-red pigmented areas over the right wrist, both elbows, both hips and both thighs. Neurological findings were limited to generalized weakness with muscle wasting and anesthesia of pigmented areas.

Laboratory studies at the time of admission revealed an erythrocyte count of 3.5 million, hemoglobin 10.5 Gm. and sedimentation rate 32 mm in 1 hour. The leukocyte count was 9,800 with 64 per cent polymorphonuclear leukocytes, 10 per cent band forms, 19 per cent lymphocytes, 6 per cent eosinophils and 1 per cent basophils. The platelet count was 320,000, bleeding time was 1 minute and coagulation time 10 minutes. Blood urea nitrogen was 17 mg. per 100 cc and serum amylase 90 units (normal 0 to 60 units).

A tentative diagnosis of diffuse vascular disease, probably periarteritis nodosa, with subacute pancreatitis was made. Initial therapy consisted of vasodilator drugs, digitalis, penicillin and narcotics as required. A skin and muscle biopsy obtained shortly after admission was reported as consistent with thromboangiitis obliterans. The patient ran a febrile course with daily temperature elevations to 103 F. A stellate ganglion block on Nov. 26, 1951, produced dubious improvement and he was started on 25 mg. of corticotropin daily by eight-hour drip. This was discontinued on Dec. 20, 1951 because of his failure to improve. During this time, he complained bitterly of pain in his left hand and precordium. Repeated electrocardiograms revealed only low voltage and sinus tachycardia with occasional extrasystoles. On Dec. 23, 1951, he wakened with right facial weakness and inability to speak. During January 1952, he experienced repeated spells of air hunger accompanied by severe left precordial pain and cyanosis. During these attacks, his pulse became feeble and rapid with a drop in blood pressure to near shock levels. On two occasions he became comatose and no pulse or blood pressure could be obtained. Consciousness returned within a few minutes. His examiners were impressed by the absence of moisture in his lungs during these episodes; this was confirmed by roentgen examination. There was marked variation in the size of his liver, which varied from 1 to 6 fingerbreadths.

During February he became progressively weaker and his course was punctuated by more frequent spells accompanied by unconsciousness. The patient noticed that his attacks could be precipitated by moving from side to side in bed. He seemed most comfortable when lying curled up on his right side. On February 19, he developed frequent episodes of rapid grunting respiration associated with increasing cyanosis, which were followed by a sudden syncopal attack from which he failed to recover.

Postmortem Findings: The heart weighed 325 Gm. Incision of the right auricle revealed a pedunculated thrombus which was attached to the endocardium of that chamber by a threadlike pedicle approximately 2 cm. in length. The thrombus was smooth, spherical and measured 3 cm. in diameter (see fig. 4). All valves were intact and normal. The coronary vessels were sclerotic with considerably narrowed lumens. Small mural thrombi were present in the apex of each ventricle. Infarcts were noted in the left lung, kidneys, spleen and left testicle. Histologic examination revealed two different processes involving the coronary arteries, one due to marked coronary atherosclerosis and the other to

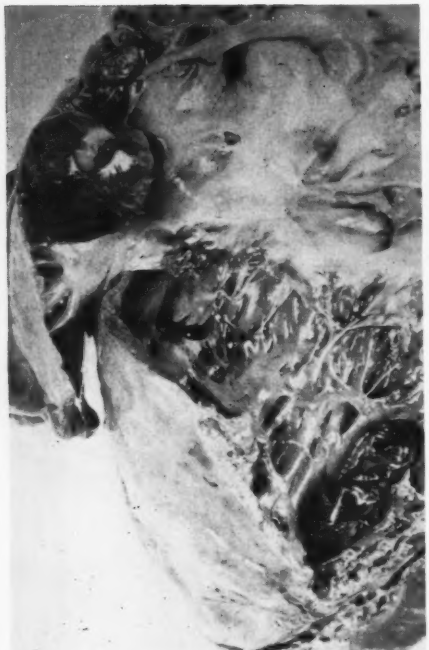

FIG. 4. The right auricle and ventricle are seen. A smooth, almost spherical thrombus, measuring 3 cm. in diameter, is suspended over the tricuspid valve by a slender pedicle. A smaller mural thrombus is seen in the apex of the right ventricle.

thromboangiitis obliterans. The myocardium was the site of diffuse fibrosis and fatty degeneration. Changes due to thromboangiitis obliterans were noted in the heart, lungs, kidneys, pancreas, adrenals, extremities, spleen and testes.

DISCUSSION OF CASES

In retrospect, the diagnosis seemed to be fairly apparent in case 1. This, however, represented our initial experience with the syndrome and we failed to review the very important observations charted in the nursing notes concerning changes in the patient's pulse with respect to postural variations. The whistling presystolic murmur was most unusual and no doubt became audible when the ball thrombus dropped into the mitral orifice, thereby simulating the effect of an extremely tight mitral stenosis. Changing murmurs are rarely observed although they have been stressed in the past by Battistini[17] and others. Covey, Crook and Rodgers[18] described a remarkable case in a 55-year-old woman who developed gangrene of the left leg concomitantly with the appearance of a loud presystolic murmur and precordial thrill. The murmur and thrill became progressively more pronounced, until finally the former could be heard a few feet from the patient. Evans and Benson[15] noted that in cases of tumor of the left auricle, a systolic murmur was most often present, although a presystolic murmur was sometimes present. The fact that the murmur disappeared during our patient's brief return to consciousness, only to recur when he lapsed back into coma, is considered especially significant by the authors.

A clinical diagnosis of occlusive thrombus was made in the second case. His repetitive episodes of peripheral vascular collapse, preceded by periods of irrational behavior, intense cyanosis about the face and lips, and inability to talk, strongly suggested the diagnosis. His profound heart failure, accelerated downhill course and shock-like state, which failed to respond to all therapeutic measures tended to reinforce the impression that an extraordinary lesion (occlusive thrombus) was present. Apart from the absence of gangrene, this patient's findings were considered rather typical of the symtomatology displayed in an ideal case of occlusive thrombosis of the left auricle.

In the third case, it was our initial clinical opinion that the patient suffered with coronary heart disease and had perhaps suffered a recent myocardial infarction with the formation of a mural thrombus. In view of the duration of his symptoms, their repetitive nature (particularly with respect to the repeated attacks of transient hemiplegia), and the unusual clinical picture presented, it was also felt that he most probably had an occlusive thrombus of the auricle, possibly originating from the site of infarction of the left auricular wall.

The fourth patient was treated on another service and was seen by the cardiovascular department early in his course with respect to his generalized vascular disease. The majority, if not all of the occlusive phenomena, were most probably explained on the basis of

thromboangiitis obliterans. The syncopal attacks preceded by complaints of "air hunger", clear lung fields, and marked variation in his liver size, fits exactly into the symptom complex of ball thrombus set forth by Wright and his colleagues.[3]

With the exception of case 4, the clinical picture presented by our patients was, in general, similar to those previously reported. In addition, we were especially impressed by the postural effects on the circulation manifested by the first and the last patient. Certainly such symptoms could not be explained on the basis of mitral stenosis per se although many of the symptoms once considered pathognomonic, such as intense cyanosis, particularly of the tip of the nose and extremities, can occur in the presence of mitral stenosis alone. We were also impressed by the occurrence of transient repetitive vascular phenomena initially limited to the central nervous system, as demonstrated by R. B., and of central nervous system manifestations preceding the onset of peripheral vascular changes, as presented by C. G. These may take the form of transient or permanent aphasia, syncopal attacks, dizziness, convulsive seizures, and hemiplegia. Usually, the central nervous system symptoms have been described as following the peripheral vascular symptoms, especially in the case of peripheral vascular collapse. Considering the vulnerability of cerebral tissue, it would seem logical to expect these symptoms to precede the peripheral symptoms. The fact that they usually do not, however, is probably related to the rapidity with which the systemic circulation is partially or completely obstructed by the thrombus. The symptom complex presented in these cases would appear to be reasonably definitive.

In view of the encouraging progress made in both the diagnosis and surgical alleviation of a variety of cardiovascular lesions, both congenital and acquired, it is probable that ultimately such thrombi may be demonstrated by angiocardiography and subsequently removed in the operating room concomitantly with a mitral valvotomy. It would appear that the first such step was taken by Bahnson and Newman[19] in 1952. They report a 54-year old woman, who when subjected to angiocardiography demonstrated a large filling defect in the right auricle. This defect proved to be produced by a large pedunculated myxoma attached to the fossa ovalis. The tumor was successfully removed at operation. The patient unfortunately succumbed 24 days later because of postoperative complications.

Summary

A review of the pertinent literature has been presented along with four new cases of occlusive auricular thrombi. Occlusive thrombi have been subdivided into (1) ball-valve thrombi, (2) pedunculated thrombi, and (3) massive thrombi. Patients with occlusive thrombi present a reasonably definitive symtom complex, manifested by peripheral and/or cerebral vascular manifestations, which are prone to be repetitive and variable. The murmurs occasionally wax and wane and all of the symptoms may be precipitated in some cases by postural variations. Two of the cases reported are notable in that one is the first reported case of pedunculated thrombus of the right auricle and the other is a case of ball thrombus occurring in a patient without mitral stenosis or rheumatic heart disease.

Summario in Interlingua

Es presentate un revista del pertinente litteratura insimul con quatro nove casos de occlusive thrombos auricular. Le thrombos occlusive es classificate como (1) thrombos globular, (2) thrombos pedunculate, e (3) thrombos massive. Patientes con thrombos occlusive presenta un satis definite complexo de symptomas apparente in peripheric e/o cerebral manifestationes vascular que tende a repeter se e a variar. Le murmures accresce e decresce a vices, e omne le symptomas pote esser precipitate in alicun casos per cambiamentos de postura. Duo del casos in iste reporto es notabile in tanto que le un es le prime unquam reportate de un thrombo pedunculate del auriculo dextere e que le altere es le caso de un thrombo globular in un patiente sin stenosis mitral e sin rheumatic morbo del corde.

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Chronic Heart Block in Dogs. A Method for Producing Experimental Heart Failure

By T. E. STARZL, M.D., PH.D. AND R. A. GAERTNER, M.D.

With the technical assistance of Elizabeth Kelley

A method is described for the production of chronic atrioventricular block in dogs, by incision of the region of the bundle of His through the open right atrium during temporary caval occlusion. Exercise tolerances, chest x-ray films, electrocardiograms, phonocardiograms, cardiac outputs, intracardiac pressures, femoral pressures, and left ventricular coronary flows were obtained preoperatively and from 1 to 10 months postoperatively. The majority of the animals developed clinical, laboratory, and pathological evidence of congestive heart failure. All animals had generalized myocardial hypertrophy.

DESPITE the inherent limitations of transferring data on experimental heart disease from animals to man, it is possible, after surgical production of lesions in animals, to make controlled analyses of various syndromes which are analogous to human disease entities. In a contemporary study in dogs[1] the acute effect of surgically induced complete heart block on cardiocirculatory function was reported. The present communication is concerned with a study of the chronic effects of complete heart block in dogs, as well as with a more detailed description of the operative procedure.

During the study, the majority of the animals with chronic complete heart block developed right and left sided heart failure, either spontaneously or after several weeks of daily exercise. Because of the current interest in developing experimental means of producing congestive heart failure, the events and details of decompensation have been described as fully as possible.

METHODS

Twelve dogs were used, ranging in weight from 10 to 23 Kg. Intravenous Nembutal was used for all pre- and postoperative catheterization studies. Postoperatively, most animals were studied once with 20 to 23 mg. per kilogram, but all other pre- and postoperative determinations were done with 27 to 30 mg. per kilogram of Nembutal.

Left ventricular coronary flow in cubic centimeters per 100 Gm. muscle per minute was measured by the nitrous oxide desaturation method[2] after catheterization of the coronary sinus and femoral artery (which was also used to record blood pressure). Cardiac output was determined by the direct Fick method, using the pulmonary artery for the mixed venous sample. A closed system spirometer, connected to an airtight endotracheal tube, was used to measure total oxygen consumption. The blood samples were analyzed for nitrous oxide by the method of Kety and Schmidt[3], and for oxygen content by the manometric method of van Slyke and Neill. Efficiency and other calculations were computed from the formulae summarized by Goodale and Hackel[2], assuming a respiratory quotient of 0.83.

Vascular pressures were detected with inductance or capacitance transducers, with electrical integration of the mean pressures when desired. The frequency response of the measuring and recording systems was in excess of 30 cycles per second when measured by recording pressures within a balloon during explosion. Electrocardiogram and vascular pressures were recorded on a direct writing oscillograph.

Specific details of other procedures are given under the appropriate sections.

RESULTS

The Technic of Surgical Production of Complete Heart Block

In 12 dogs, under ether anesthesia after morphine-atropine premedication, section of the region of the bundle of His was carried out. Permanent complete heart block was obtained in every case. One animal died on the third postoperative day, and all others

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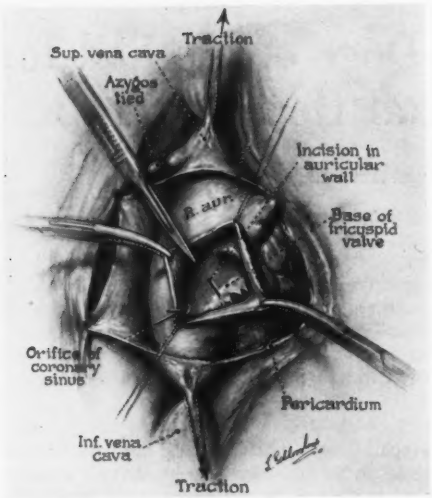

FIG. 1. Artist's view of the technique for surgical production of complete heart block. The auricle has been entered during temporary caval occlusion, and the cut made across the auriculoventricular junction at the posterior end of the base of the septal cusp.

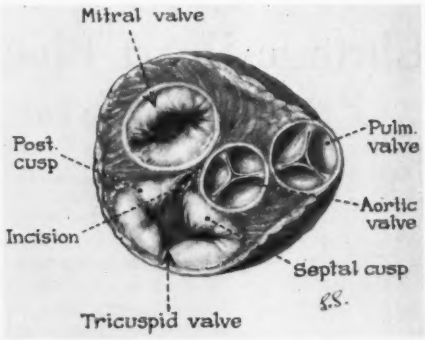

FIG. 2. Details of the anatomy of the intracardiac incision for heart block. The auricles have been removed, and the view is from above. Note the relation of the cut to the posterior end of the septal cusp, the left auricle, and the base of the aorta.

survived for chronic study. The heart was approached through a thoracotomy in the right fourth costal interspace. Operative details are shown in figure 1. The azygos vein was ligated, and braided silk placed around the superior and inferior venae cavae, extrapericardially. The pericardium was opened anterior to the phrenic nerve. Arterial silk sutures were placed at the superior and inferior extremities of the proposed auricular incision, and the intervening auricular wall grasped in a curved noncrushing clamp. The auricular wall isolated by the clamp was incised. The cavae were occluded by traction on the braided silk, and the auricle entered. Residual blood in the right side of the heart and continuing drainage from the coronary sinus was sucked out and an incision was made across the auriculoventricular junction 5 to 10 mm. anterior to the coronary sinus (fig. 1). The cut was begun at the posterior end of the base of the septal cusp, and usually extended for a short distance into the contiguous auricle and ventricle. The relations of the incision at the auriculoventricular junction are shown in figure 2. It was similarly found by Erlanger and Blackman[4] that complete heart block could be most easily produced by injury to the region illustrated.

Usually it was possible to be sure at what moment heart block was established for auriculoventricular dissociation was obvious even though the cavae were occluded, and the right side of the heart empty of blood. In all animals, a spontaneous ventricular beat began immediately, and ventricular asystole at the operating table was never observed.

In most cases complete heart block was obtained during a single entry into the auricle with a total caval occlusion time of 50 to 60 seconds. In some animals in which block was not readily produced, it was necessary to reenter the heart several times to deepen or extend the cut. This was attended with an increased risk of accidental septal defects, and in 4 of the 12 dogs small communications were made through the membranous portion of the interventricular septum or through the low interauricular septum. (See relations in fig. 2.) These defects were recognized by the presence of bright red blood in the base of the cut, and were closed immediately, usually by a single suture. In these instances in which complete block was obtained with some difficulty, multiple caval occlusions for short periods were well tolerated, and were not accompanied by any increase in postoperative difficulties.

At the conclusion of the intracardiac procedure, the cavae were released, allowing the right heart to fill with blood before placing the noncrushing clamp back on the auricular incision. The auricular wall was then closed with continuous over and over silk. With the slowed rate of complete block, the heart could be observed to be dilated, so markedly that the pericardium was generally not closed. X-ray films, taken immediately and for as long as the animals lived, revealed an invariable enlargement of the cardiac shadow (fig. 3).

The unanesthetized preoperative resting pulse rates of the animals in this study were from 90 to 140 per minute. After complete heart block, rates under the same conditions ranged from 30 to 65 per minute. Seven of the

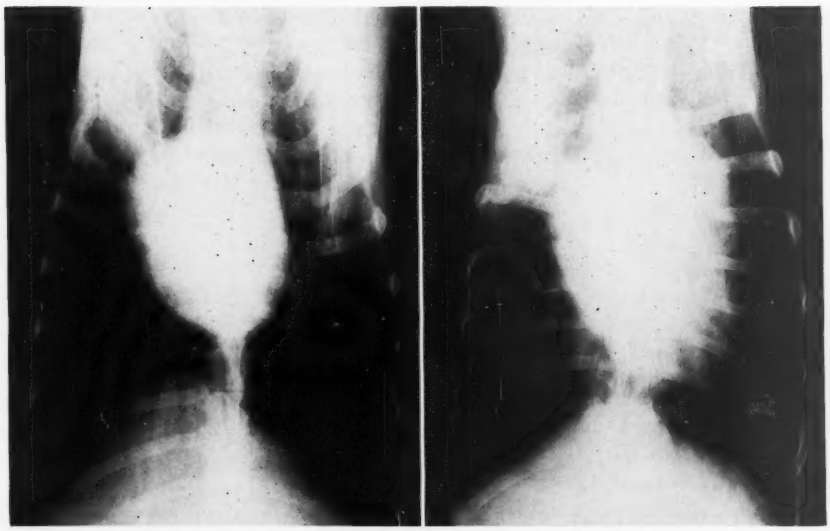

FIG. 3. Two-meter chest x-ray films preoperatively (left), and 12 days after performance of surgical complete heart block (right). Preoperative rate was 120 per minute and idioventricular rate was 40 per minute. Note cardiac enlargement and pulmonary vascular congestion after block.

11 dogs studied chronically had rates between 40 and 55 per minute, two animals consistently running lower and two higher rates than this usual range. The resting rate which prevailed for the balance of any dog's life had generally become evident within 48 hours, and remained about the same from day to day and month to month. It was not possible to explain the differences in the fundamental ventricular frequency within this group of dogs on the basis of different location of lesions, since all the cuts were made in essentially the same area.

It has been shown that the cardiac output of dogs is considerably reduced immediately after the surgical production of complete heart block (1, 5). This explains the clinical behavior of the dogs during the first two to seven days. They were easily fatigued, could be made to ambulate only with difficulty, and were so lethargic that an assisted feeding and watering program had to be initiated in several instances. The keynote of postoperative therapy was avoidance of situations which might tax an already dangerously low cardiac output. Water seal drainage was used in closing the thoracotomy, and vigilance was maintained for signs of pneumothorax and atelectasis. Heavy doses of antibiotics were given, since it was noticed early that even a superficial wound infection had a surprisingly detrimental effect on recovery. Activity was discouraged. The phlegmatic behavior characteristic of the early postoperative period gradually disappeared and after a week or 10 days it was difficult with casual observation to distinguish these animals from normal dogs.

Electrocardiographic confirmation of the complete heart block was obtained at frequent intervals postoperatively. It was possible, in addition, to study the auriculoventricular dissociation stethoscopically. Audible auricular sounds, at two and one-half to four times the frequency of the regular heart sounds, could be heard widely over the chest, most prominently at the anterior extent of the fourth intercostal space on the left. These auricular sounds were present in every animal. They were loudest immediately after surgery, and became fainter with the passage of time. The sounds were intensified after exercise, and softest during rest. Spectral phonocardiograms, which allow visualization of time, frequency, and intensity of heart sounds[6, 7] were obtained in six of the dogs at 2 to 300 days after the performance of

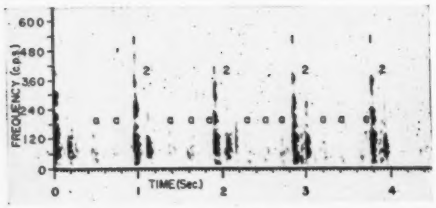

FIG. 4. Spectral phonocardiogram of dog which had been completely blocked for four months. The auricular sounds (a) seen in the record were easily detectable upon stethoscopic examination, although softer than the regular heart sounds (1, 2).

block.* An example is shown (fig. 4) in which by critical filtering, the auricular and ventricular sounds are boldly contrasted in a dog which had been blocked for four months. In several dogs, a prominent auricular diastolic murmur was detected on the spectral phonocardiogram in conjunction with the auricular sounds. The characteristics of this murmur were quite like those of a similar murmur described by Rytand in elderly patients with heart block.[8]

Clinical Course of Animals Which Developed Heart Failure

After the first few days of extreme lethargy, the blocked dogs began to eat well (diet consisted of standard grain-base dog meal) and superficially seemed normal. That complete compensation had not uniformly occurred, however, was evident from the fact that 5 of the 11 dogs studied chronically developed congestive heart failure within three months, essentially at cage rest, and two others failed later under the stress of controlled daily exercise. The animals with the slowest idioventricular rhythms were somewhat more prone to develop heart failure than dogs with faster rates, although this was not consistently the case. Of greater importance in the genesis of decompensation was the degree of spontaneous physical activity exhibited by the subject. For example, the dog which was observed for the longest time (10 months) had a resting rate of 30 to 35 beats per minute throughout his life, was slothful and never developed evidence of heart failure. The dog which first developed failure in this series (two weeks) had a rate of 65, but was hyperactive in the cage. The onset of symptoms and signs of heart failure occurred from 2 to 16 weeks after surgery and developed after the interlude of apparent adjustment described above. The first notable alteration was generally a return of the lassitude and anorexia which had been present immediately after surgery. Hepatomegaly could soon be detected, followed by ascites. Prolonged dyspnea followed the slighest exertion. Chest x-ray films usually showed pulmonary vascular congestion (fig. 3), a finding which in some cases was the first indication of impending failure.

Although there was evidence of both right and left heart failure, development of signs of right sided failure always dominated the ultimate picture, and terminally hepatomegaly and ascites were far more advanced than pulmonary edema and pleural effusion. The course of the decompensation was relatively benign. Only one of the seven dogs which decompensated died spontaneously. The rest were either sacrificed, or died as the result of accidents in catheterization or treadmill exercise. The majority of these animals were in mildly progressive failure for at least six weeks before their death.

To determine with certainty that the heart failure was primarily related to the lesion in the conduction system, rather than to nonspecific effects of the surgical procedure, six dogs were subjected to "sham" operations in which every step was taken except the actual section of the bundle of His. The animals were watched from three to six months, and none had any pre- or postmortem suggestion of heart failure.

The Effect of Chronic Heart Block on Vascular Pressures

It has been shown that the right auricular pressures of dogs with surgically induced complete heart block are only moderately elevated in the early postoperative period.[1] In the present series in which observations were started later, the dogs which developed clinical and pathological evidence of heart failure showed large increases in right auricular pressure to levels as high as 220 mm. H_2O. These rises were present in some cases at the end of the month, and in others appeared later (fig. 5),

* Spectral phonocardiography and analysis were done by Dr. Victor A. McKusick.

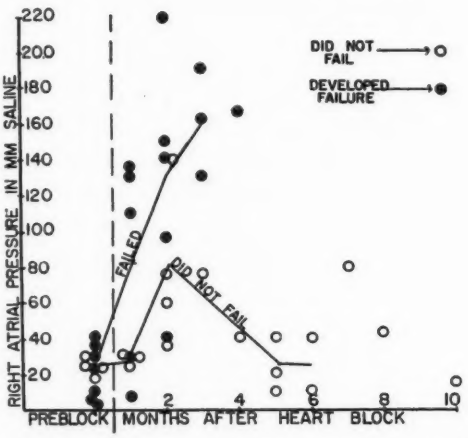

FIG. 5. Right atrial pressures in dogs with complete heart block, the open circles representing measurements from animals which did not fall, and the black dots being from animals which decompensated.

coinciding with the onset of clinical signs of decompensation. The pressure configuration (fig. 6*C*) did not suggest a significant tricuspid regurgitation in any of these dogs. The animals which did not develop heart failure either never had large rises in right auricular pressure or had early elevations which subsequently returned to relatively normal values (fig. 5).

With the extreme bradycardia of complete heart block, right ventricular ejection pressures were high, ranging from 40 mm. Hg to 70 mm. Hg (fig. 6*B*). The contribution of auricular systole to ventricular diastolic filling was demonstrable in every animal (fig. 6*B*). With the onset of failure the pressure rise during

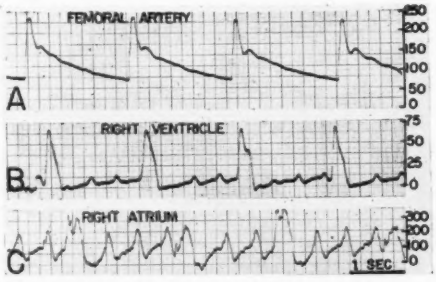

FIG. 6. Femoral arterial *A*, right ventricular *B*, and right atrial *C* pressures. Calibrations of the first two are in millimeters Hg and of the third in millimeters water. The records are all from animals in heart failure.

diastole became steeper and the auricular pressure waves more prominent. The example shown (fig. 6*B*) is from a decompensated animal in which the end diastolic pressure is 130 to 160 mm. H_2O. The pressure with ventricular systole returned to 0 in every animal except one (who was in far advanced failure), and in this exceptional case the end systolic pressure was 5 to 7 mm. Hg.

The femoral pulse, by palpation, was full and almost pistol shot in the dogs with the slowest rates. Direct arterial pressure recording generally showed an elevation of systolic pressure, with a wide pulse pressure (fig. 6*A*). In the case shown, the pressure was 230/80 mm. Hg. Mean blood pressure was in general slightly less than had been obtained in the preoperative controls (fig. 7). Significant differences in the arterial pressure levels, between the animals which failed and those which did not, could not be detected (fig. 7).

The Effect of Chronic Complete Heart Block on Exercise Tolerance

Before surgery, the exercise capacity of the dogs was obtained by use of a treadmill.[9] A level running surface was used with a standard speed of 7 miles per hour. Tolerance was defined as the duration of running necessary to cause the dogs to collapse, and in the controls ranged from one to three hours.

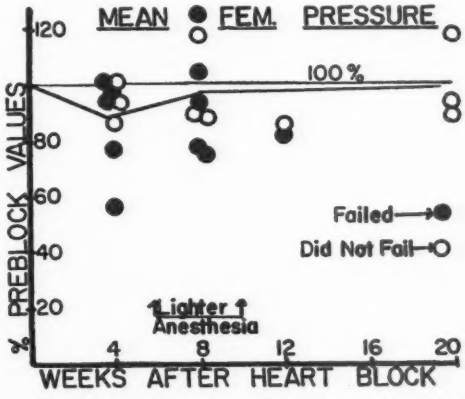

FIG. 7. Mean femoral arterial pressures in animals with chronic complete heart block, expressed in per cent of preoperative controls (each animal thus serving as its own control). Note lack of correlation of values to presence or absence of heart failure.

Postoperatively, eight of the animals were tested monthly for exercise tolerance. During the first three months no exertion was allowed other than that necessary for the actual testing. At the end of three to four months, three of the eight animals had developed clinical signs of heart failure. At this time the remaining five animals were placed on a regimen of daily severe exercise. With this enforced exertional stress, two more animals developed heart failure, primarily right-sided, within two weeks. Both of these dogs died while running on the treadmill, in one case with rupture of a remarkably congested liver. The remaining three dogs were continued with daily exercise for five weeks, and far from developing any signs of decompensation, seemed to get stronger.

One month after the heart block, the exercise tolerance was greatly reduced in every animal, somewhat more severely in the animals which were failing or eventually failed (fig. 8). Endurance at this time ranged from 2 to 25 minutes. The animals which never developed heart failure manifested a steady return of exercise capacity, until at the end of four months they could run about as well as before the block (fig. 8). In contrast the animals which were failing or ultimately failed had no such restitution of exercise tolerance, which remained low until death (fig. 8).

The pulse was counted before and after each treadmill determination. Rate usually increased 10 to 20 beats per minute during the run. The femoral pulse became much more forceful during and after exercise.

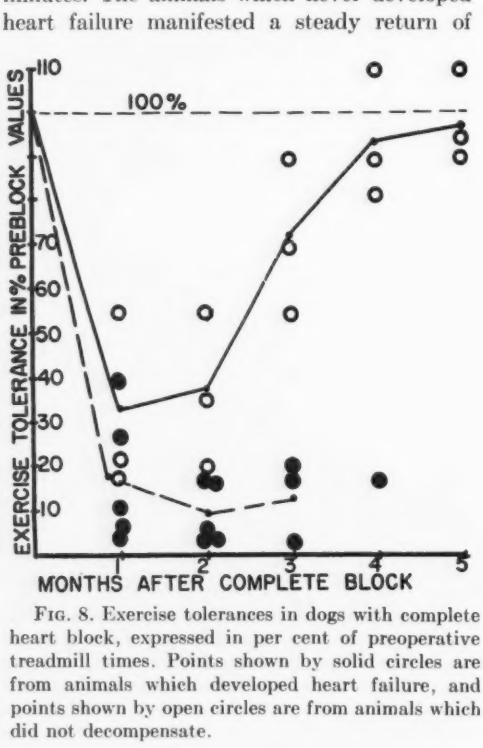

FIG. 8. Exercise tolerances in dogs with complete heart block, expressed in per cent of preoperative treadmill times. Points shown by solid circles are from animals which developed heart failure, and points shown by open circles are from animals which did not decompensate.

The Effect of Chronic Heart Block on Cardiac Output

Prior to surgery, cardiac outputs were obtained in nine of the dogs, using a Nembutal dose of 27 to 30 mg. per kilogram. After four weeks of complete heart block, cardiac outputs were again obtained under the same anesthetic conditions. Despite large stroke volumes of from 40 to 80 cc. the outputs were generally reduced both in the animals which failed and in those which remained compensated (fig. 9). At the end of eight weeks, cardiac output studies were

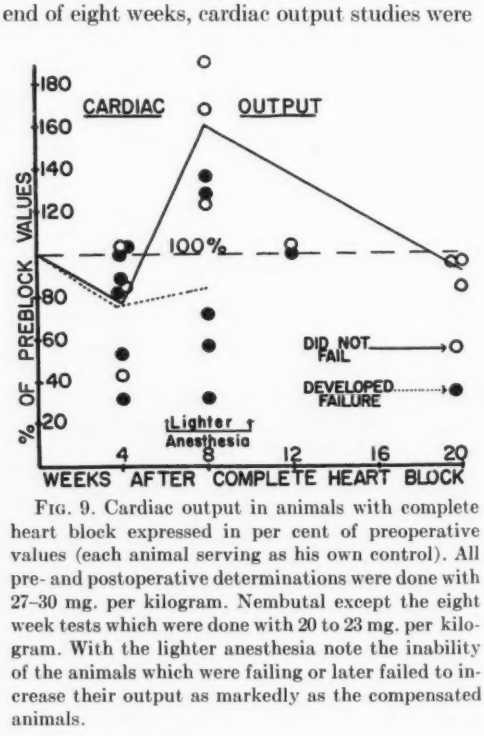

FIG. 9. Cardiac output in animals with complete heart block expressed in per cent of preoperative values (each animal serving as his own control). All pre- and postoperative determinations were done with 27–30 mg. per kilogram. Nembutal except the eight week tests which were done with 20 to 23 mg. per kilogram. With the lighter anesthesia note the inability of the animals which were failing or later failed to increase their output as markedly as the compensated animals.

again done, this time with 23 mg. per kilogram of Nembutal, an anesthetic alteration which in normal animals would be expected to increase the minute output of the heart. Under these new conditions, the animals which did not fail responded with large increases in cardiac output (fig. 9). The ventricular rates under the two levels of Nembutal anesthesia were about the same in any animal, so the rises in output were primarily due to stroke volume increases. Dogs which were failing or eventually failed either had output gains which were smaller than those of the compensated animals, or had no increases at all (fig. 9).

The Effect of Chronic Complete Heart Block on Left Ventricular Coronary Flow, Efficiency, Oxygen Consumption, and Work

In previous studies on the early effect of complete heart block in dogs, it was demonstrated that changes in coronary flow and left ventricular oxygen consumption rather closely paralleled alterations in the generally reduced left ventricular work, with little consequent alteration in calculated myocardial efficiency.[1] In the present study, similar determinations were done in eight dogs. Preoperative left ventricular weights, for use in the calculation of efficiency and left ventricular oxygen consumption, were estimated by the method of Goodale and Hackel.[2] Because hypertrophy developed after heart block, the measured postmortem weights of the left ventricular were used for all postoperative computations.

The results in the present series were similar to the acute studies, with two noteworthy exceptions which can be shown most clearly by demonstrating the interrelationships in a single case (fig. 10). In contrast to the earlier studies,[1] the left ventricular work in the present series returned to preblock levels in some cases. When this occurred, and the animals were not in congestive failure, the coronary flow and left ventricular oxygen consumption were reduced in relation to the work done with a resultant increase in myocardial efficiency (fig. 10—see values at four weeks), a change probably explicable on the basis of the slowed rate.[10, 11] In the animal shown, heart failure subsequently developed. With the onset of failure, coronary flow and left ventricular oxygen consumption increased despite a relatively unchanged work load leading to a marked fall in myocardial efficiency. All failing animals studied in the present series were characterized by declining efficiencies, a finding which is in agreement with considerable previous information on decompensation in heart-lung preparations[10, 12] and in intact organisms.[13, 14]

Effect of Chronic Heart Block on Heart Weight

At autopsy the total heart weights were measured by the method of Herrmann[15] in 10 of the 11 dogs followed chronically. All animals had been blocked for at least six weeks, and the oldest had been blocked for 10 months. The total heart weights were greater by 5 to 50 per cent than predicted on the basis of body weight

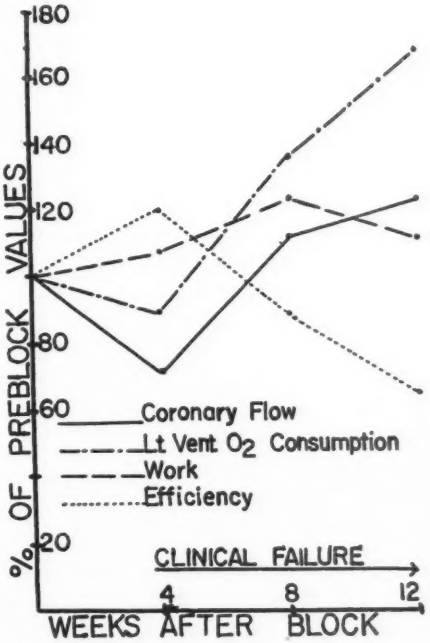

FIG. 10. Left ventricular coronary flow, work, oxygen consumption, and efficiency before (four week determination), and after the onset of congestive heart failure (8 and 12 week determinations). Note the progressive fall in efficiency after decompensation, from a level which was initially higher than obtained in the preoperative control.

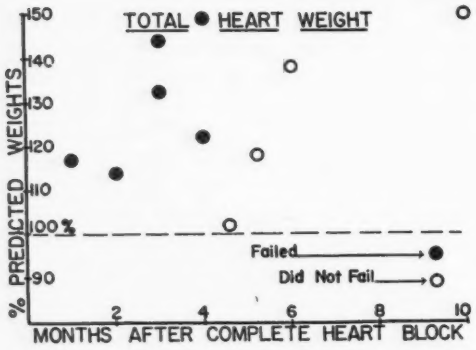

FIG. 11. Total heart weights of dogs with complete heart block, in per cent of values predicted by method of Herrmann. Note absence of correlation between the degree of hypertrophy and the presence or absence of heart failure.

with the Herrmann coefficient (fig. 11), a hypertrophy somewhat less extreme than described by Erlanger and Blackman.[16] The degree of hypertrophy, within the time limits of six weeks to 10 months, was not clearly related to the longevity of the block, and was not significantly related to the presence or absence of heart failure (fig. 11).

The ventricles were then measured after dissection by the method of Goodale and Hackel,[2] and in every case left ventricular weight was greater than expected from the Goodale-Hackel coefficient.

Finally, in order to gain an idea of the relative hypertrophy of the different cardiac chambers, further division was carried out by Herrmann's technique in five hearts, and the weights compared with those expected from Herrmann's predictions. Both ventricles were found to be hypertrophied (fig. 12), the left slightly more than the right. The weight ratios of left to right ventricles were somewhat increased also (fig. 12), suggesting a slight predominance of left ventricular hypertrophy. The auricles, incidentally, were also increased in weight.

Postmortem Findings

Postmortem examinations were conducted on all animals immediately after death, excluding the head in all but two cases. Microscopic

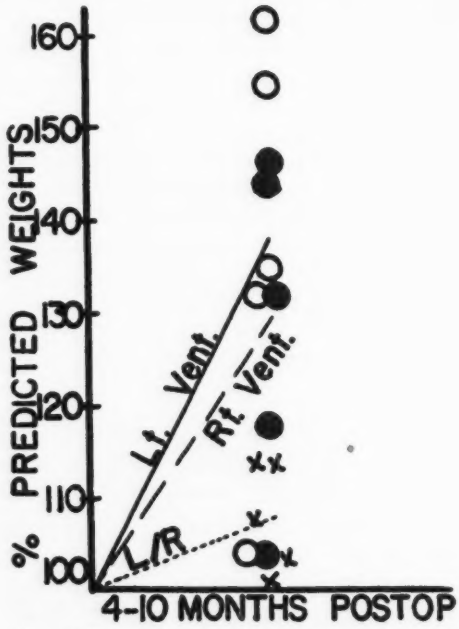

FIG. 12. The ratio of left to right ventricular weight (L/R) in per cent of the values predicted by the method of Herrmann. The changes in left (Lt. Vent.) and right ventricular (Rt. Vent.) weight are also shown. Solid circles represent left ventricular weights, crosses represent L/R ratios, and open circles represent right ventricular weights.

sections* were made of the lungs, heart, liver, kidney, adrenals, small bowel, aorta, and in two dogs (both of which were decompensated) the pituitary. The positively abnormal findings, which histologically were limited to the liver and lungs, are summarized in table 1.

Particular care was taken, in the gross examination of the hearts, to rule out the possibility that valvular damage, unrealized septal defects, or postoperative constrictive pericarditis might have played a role in the production of the symptoms and signs of congestive heart failure. None of these factors could be implicated. Pericardial adhesions were filmy or absent. No septal defects were present. All valves were found on testing to be functionally competent, and indeed no changes could be detected in any valve except the tricuspid which

* Histologic examinations were done by Dr. William Rienhoff, III.

TABLE 1.—*Gross and Microscopic Changes in Animals with Complete Heart Block. All Chronic Animals had, in addition, Generalized Cardiac Hypertrophy. Specific Mention is Made only of Positive Findings*

No.	Duration of Complete Heart Block	Gross	Microscopic	Remarks
1	12 weeks	100 cc pleural effusion; 900 cc ascites; pulmonary edema; enlarged congested liver	Diffuse pulmonary edema with many hemosiderin-laden macrophages in alveoli; chronic passive congestion of liver	Dog had terminal acute pyelonephritis
2	43 weeks	Normal	Normal	Sacrificed
3	3 days	Focal atelectasis of lungs	Focal atelectasis of lung	During operation IA defect made and closed. Postop animal had signs of brain damage, probably from air embolus. No brain post done
4	14 weeks	Equivocal pulmonary edema; 100 cc ascites; enlarged congested liver	Acute and chronic passive congestion of liver	Died suddenly during tread mill run
5	6 weeks	Liver enlarged and congested	Chronic passive congestion of liver	Fibrillated during catheterization
6*	14 weeks	1200 cc mixed blood and ascitic fluid. Liver enlarged and congested. Liver had linear rupture	Intrahepatic hemorrhage. Acute and chronic passive congestion of liver	Died during treadmill run
7	8 weeks	550 cc pleural effusion; pulmonary edema; 2050 cc ascites; large congested liver	Pulmonary edema; Chronic passive congestion of liver	Fibrillated during catheterization
8	22 weeks	Normal	Normal	Sacrificed
9	10 weeks	50 cc pleural effusion; 200 cc ascites; extensive retroperitoneal edema; pulmonary edema; large congested liver	Patchy pulmonary edema with hemosiderin laden macrophages in alveoli; chronic passive congestion of liver	Sacrificed
10	12 weeks	40 cc pleural effusion; 900 cc ascites; pulmonary edema; enlarged congested liver	Many hemosiderin-laden macrophages in lung but no demonstrable edema fluid; chronic passive congestion of liver	Sacrificed
11	21 weeks	Normal	Normal	Sacrificed
12	18 weeks	Normal	Normal	Sacrificed

* Failure precipitated by daily treadmill exercise.

in some animals had minor scarring at the point where the intracardiac incision had been made.

The four animals which had not developed clinical or laboratory signs of heart failure had no pathological abnormalities except for the hypertrophy noted above. The seven animals which had decompensated all had unmistakable changes (table 1). All seven had chronic passive congestion of the liver, characterized grossly by enlargement and nutmeg appearance on section, and microscopically (fig. 13) by central lobular atrophy, distention of the sinusoids, and varying degrees of fibrosis. Five had significant ascites. Four of the dogs had small or moderate pleural effusions. In five cases gross pulmonary edema was seen. Microscopically, hemosiderin-laden macrophages were present within thick-walled pulmonary alveoli in four animals, and in three cases pulmonary edema fluid was unequivocally present (fig. 13).

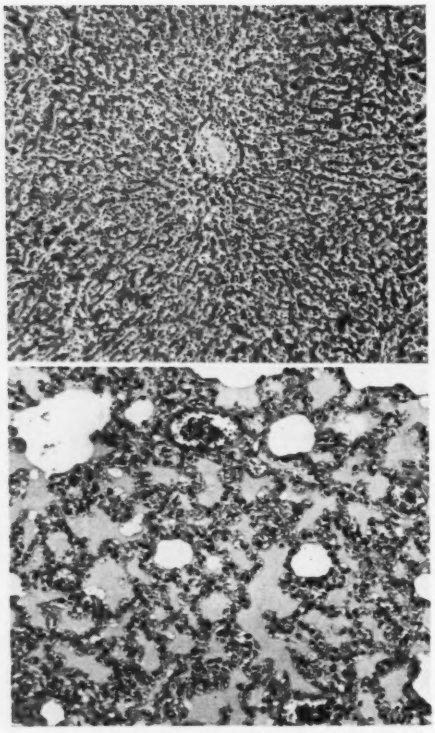

FIG. 13. Sections of the liver (upper) and lung (lower) showing central lobular atrophy and pulmonary edema. (liver (upper) × 75 lung (lower)– × 150).

DISCUSSION

Chronic heart block in dogs is a preparation of experimental utility from several points of view. It affords a means of studying bradycardia. Blocked hearts are parasympathetically denervated as far as rate control is concerned,[1, 17] although sympathetic stimulation can cause minor rate increases.[17] Since in this and other respects the situation is more like a Starling heart-lung preparation than is the case in the intact animal, it is possible to obtain accurate information on *in vivo* stroke volume adjustments to alterations in rate[1, 18] and output demand. Complete heart block shortly induces a generalized, although slightly asymmetrical hypertrophy. Finally, it is a preparation which leads to right and left sided congestive heart failure. In this series, decompensation occurred in the majority of animals, and it is felt that if the animals had been exercised during the first few postoperative weeks most or all would have failed.

There is much evidence that the congestive heart failure is specifically due to the conduction defect (and the resultant bradycardia) rather than to any nonspecific effect of the operative procedure. At autopsy, essentially no deformation of normal anatomy could be demonstrated either within or around the heart. "Sham" operations were followed by quick and uneventful recoveries. Finally, in the classic work by Erlanger and Blackman,[16] chronic heart block in dogs produced by a different technique likewise resulted in several instances of heart failure.

In several respects, chronic heart block presents a uniquely advantageous situation for the study of events of low output cardiac failure. There is a discrete onset of reduced cardiac output[1, 5] following which a considerable time intervenes before large elevations occur in central venous pressure and before clinical signs of decompensation become manifest. The excessive and inadequately managed stroke work load is not regionally imposed upon selective areas of the heart as shown by the general hypertrophy and the evidence of both systemic and pulmonary vascular congestion. Changes in the myocardial metabolism, in the direction of impaired myocardial efficiency, are in accord with the classic concept of cardiac decompensation.[10, 12]

Space does not allow a detailed comparison between complete heart block in dogs and in man, although general clinical opinion indicates that this entity is better tolerated in humans than might be inferred from the present study in dogs. However, Erlanger's analysis of the striking similarity of this condition in the two species[17] suggests that the present data in dogs may have some application to the analogous human syndrome, at least in arriving at a better understanding of the directional changes which occur with bradycardia.

SUMMARY

A method has been described for the surgical production of chronic complete heart block in

dogs. This consists of incision of the region of the bundle of His through the open right auricle during temporary occlusion of the vena cavae. Exercise tolerances, chest x-ray films, electrocardiograms, phonocardiograms, cardiac outputs, intracardiac pressures, femoral pressures, and left ventricular coronary flows were obtained preoperatively and from 1 to 10 months postoperatively. The majority of the animals developed clinical, laboratory, and pathological evidence of heart failure either spontaneously or after a period of enforced treadmill exercise. The congestive failure was characterized by an elevated central venous pressure, reduced cardiac output, falling myocardial efficiency, hepatomegaly and cardiac cirrhosis, ascites, pulmonary vascular congestion, and pulmonary edema. All animals had generalized myocardial hypertrophy.

Acknowledgment

It is a pleasure to acknowledge the influence and direction of Dr. Alfred Blalock in this study, both in its inception and progress.

Summario in Interlingua

Es describite un methodo pro le production chirurgic de chronic bloco cardiac complete in canes. Le methodo consiste in executar un incision in le region del fasce de His a transverso le aperite auricula dextere durante le occlusion temporari del vena cave. Le sequente studios laboratorial esseva executate ante le operation e a periodos de inter 1 e 10 menses plus tarde: tolerantia a exercitios, roentgenogramma thoracic, electrocardiogramma, phonocardiogramma, rendimento cardiac, pression intracardiac, pression femoral, e fluxo ventriculo-coronari sinistre. Le majoritate del animales disveloppava signos clinic, laboratorial, e pathologic de dysfunctionamento cardiac, o spontaneemente o post un periodo de exercitio fortiate. Le dysfunctionamento congestive esseva characterisate per le sequente tractos: elevate pression venose central, reduction del rendimento cardiac, abassate efficacia myocardiac, hepatomegalia e cirrhosis cardiac, ascites, congestion pulmono-vascular, e edema pulmonar. Omne le animales habeva generalisate hypertrophia myocardiac.

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The Effect of Hyperventilation on Various Arrhythmias

By D. Scherf, M.D., M. Goldfarb, M.D. and R. Bussan, M.D.

The influence of hyperventilation on various cardiac arrhythmias is examined. Auricular and ventricular extrasystoles disappear temporarily, paroxysmal auricular and ventricular tachycardias as well as attacks of short paroxysmal auricular fibrillation are abolished by hyperventilation. An attempt is made to explain these phenomena.

ALTERATIONS of RS-T segment and of the T waves of the electrocardiogram have been described as a consequence of hyperventilation.[5, 13] This, however, is controversial, since such changes were not seen by other investigators,[11] provided hyperventilation was performed in such a manner that a marked increase of the sinus rate was avoided and the respiration was not so shallow and rapid as to cause anoxia.

One of us observed a patient for several years who was subject to long paroxysms of auricular ectopic tachycardia. Hyperventilation in this patient was followed by a conspicuous reduction in the number of ectopic beats.[12] There are no other studies known to to us on the influence of hyperventilation on arrhythmias of various types. The present report deals with an investigation of the response of arrhythmias to hyperventilation. We do not propose to present a statistical analysis of the frequency of the changes since the series is too small; our report will be confined to the presentation of a few positive cases.

Method

Following the registration of control electrocardiograms the patients were instructed to hyperventilate by maximal inspiration and expiration. Care was taken to insure that the respiratory rate did not increase materially. If, as is often done, the patient is told to increase depth and rate of respiration "as much as possible"[5] or to breathe "as rapidly as possible"[13], hypoxia of the myocardium is unavoidable since the volume of tidal air with this type of breathing is so reduced that the exchange of air involves mainly the dead space and does not contribute much to the exchange of gases in the lungs.

At the appearance of a Chvostek or Trousseau sign, normal respiration was substituted for hyperventilation. Electrocardiograms were repeated every minute during hyperventilation and for about 10 minutes thereafter. If significant alterations in the existing arrhythmias appeared during hyperventilation, the entire procedure was repeated whenever possible in order to exclude the possibility of a coincidence.

Effects of Hyperventilation on Various Arrhythmias

Auricular Extrasystoles

E. S. was a 72 year-old woman. All records are reproduced from lead II. The top tracing (*A*) in figure 1 shows a sinus rhythm interrupted by short attacks of auricular fibrillation. In some areas the tracing resembles one of multiple auricular extrasystoles but the diagnosis of fibrillation is justified by irregularly formed F waves in several parts of the tracing. Hyperventilation was performed for five minutes before a Chvostek sign appeared. The sinus rate was unaffected and remained 90 to 100 beats per minute before and after hyperventilation. The disturbance of rhythm disappeared completely and a regular sinus rhythm prevailed (fig. 1*B*). Five minutes later auricular extrasystoles returned (fig. 1*C*) and short attacks of fibrillation recurred. After another five minute period of hyperventilation sinus rhythm reappeared (fig. 1*D*). Ten minutes after the second period of hyperventilation the electrocardiogram (fig. 1*E*) showed the same pattern as the control (fig. 1*A*).

In this patient hyperventilation abolished the extrasystoles and short attacks of auricular fibrillation without changing the rate of the basic sinus rhythm.

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Dr. Bussan is a Trainee of the National Heart Institute.

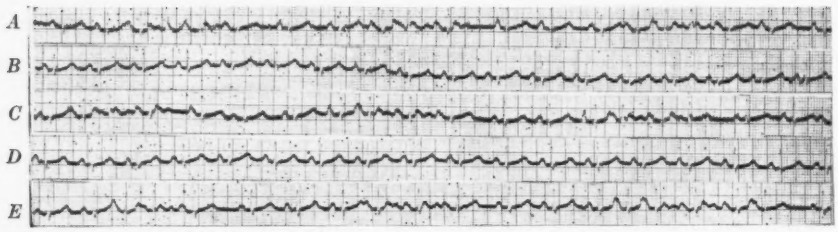

FIG. 1. Lead II. (*A*) shows auricular extrasystoles and short attacks of auricular fibrillation before hyperventilation. Sinus rhythm appeared after hyperventilation (*B*). Five minutes later extrasystoles and fibrillation returned (*C*) but disppeared again after a second period of hyperventilation (*D*). (*E*) shows the return of the arrhythmias 10 minutes later.

Ventricular Extrasystoles

J. R., a 53 year-old male, suffered from coronary sclerosis and was hospitalized because of congestive heart failure. During the course of digitalis therapy ventricular extrasystoles appeared and exhibited characteristic, continuous changes of form (fig. 2*A*). The electrocardiograms shown were recorded in lead III.

Hyperventilation was performed until a Chvostek sign appeared. This led to complete disappearance of the extrasystoles (fig. 2*B*). In this instance, as in the previous case, the sinus rate was not affected by the hyperventilation and remained at 110 beats per minute. Within five minutes after the hyperventilation was discontinued the ventricular extrasystoles reappeared (fig. 2*C*), but renewed hyperventilation for five minutes again abolished them (fig. 2*D*). Two and one-half minutes after the second hyperventilation ceased ventricular extrasystoles of varying forms were again evident in the electrocardiogram (fig. 2*E*).

S. L., a 57 year-old male, was admitted because of coronary sclerosis. He had received digitalis for congestive heart failure. The tracings illustrated were recorded in lead III. Before hyperventilation the pattern of left bundle-branch block with multiform ventricular extrasystoles was recorded (fig. 3A). After four minutes of hyperventilation, which produced a Chvostek sign, a regular sinus rhythm occurred (fig. 3*B*). The rate was 60 before hyperventilation and 55 afterward. Following hyperventilation electrocardiograms were taken at one minute intervals. After seven minutes (fig. 3*C*) the same arrhythmia seen in figure 3*A* has recurred.

In one patient who had both auricular and ventricular extrasystoles, the ventricular ones dis-

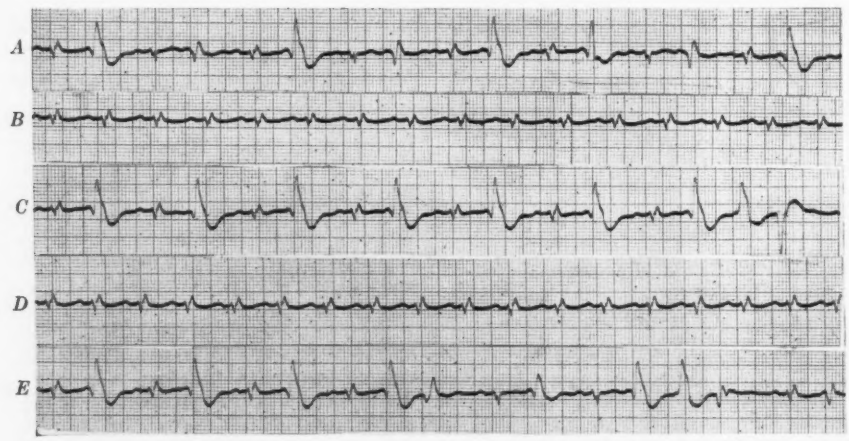

FIG. 2. Lead III. (*A*) shows regularly appearing ventricular extrasystoles (bigeminy) due to digitalis therapy. The extrasystoles disappear after hyperventilation (*B*), and recur 5 minutes after discontinuation of the hyperventilation (*C*). A second period of hyperventilation lasting five minutes abolishes the extrasystoles again (*D*). They appear again two and one half minutes later (*E*).

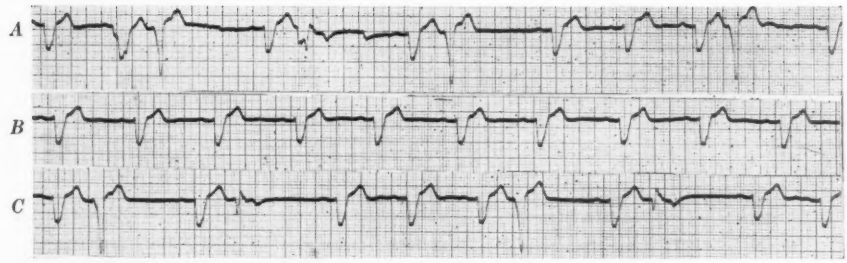

FIG. 3. Lead III. (*A*) reveals multiform ventricular extrasystole with left bundle branch block. The extrasystoles disappear after four minutes of hyperventilation (*B*) and reappear seven minutes after the end of hyperventilation (*C*).

appeared with hyperventilation but the auricular ones persisted.

In 13 other cases of extrasystoles, hyperventilation seemed to exert no influence in nine.

Paroxysmal Auricular Tachycardia

The hyperventilation experiment was performed on 16 patients with paroxysmal auricular tachycardia, but proved successful in only the one case which follows.

M. B., a 50 year-old male, was admitted with a long history of paroxysmal tachycardia, emphysema and rheumatoid arthritis. During one attack of paroxysmal tachycardia hyperventilation was attempted for eight minutes, but the patient cooperated poorly and a Chvostek sign failed to appear. No changes were observed in the attack and the patient refused to continue. He was discharged and returned in two months, claiming to have stopped many attacks by hyperventilation. When readmitted he had auricular tachycardia with a rate of 200 beats per minute (fig. 4*A*). The patient was actively hyperventilating for some time and could not be made to stop. About 20 seconds after figure 4*A* was taken, the attack stopped (fig. 4*B*). Only auricular extrasystoles were recorded. One minute later the attack recurred (fig. 4*C*), beginning with aberrant auricular extrasystoles. The patient could not be persuaded to hyperventilate again.

Paroxysmal Ventricular Tachycardia

S. V., a 72 year-old male, was admitted with the diagnosis of coronary sclerosis and auricular fibrillation. He had received moderate doses of digitalis. A ventricular tachycardia appeared which, because of the constant form of the ventricular complexes, could not be attributed, with certainty, to digitalis (fig. 5*A*). The rate of the tachycardia was 166 beats per minute. Hyperventilation lasting eight minutes led to the disappearance of the tachycardia (fig. 5*B*). Only a short series of extrasystoles appeared with a rate of 115. Three minutes after the end of hyperventilation the tachycardia had reappeared (fig. 5*C*). The rate was again 166. Hyperventilation, this time for nine minutes, again interrupted

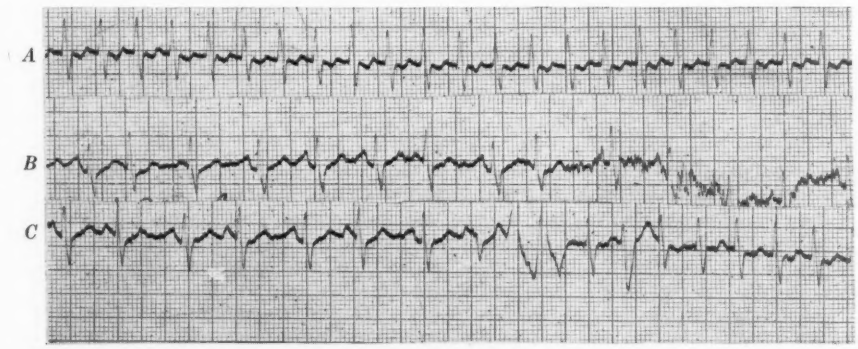

FIG. 4. Lead II. (*A*) shows a regular paroxysmal auricular tachycardia. The attack stopped during hyperventilation (*B*) and only single auricular extrasystoles appeared. One minute later the attack recurred (*C*).

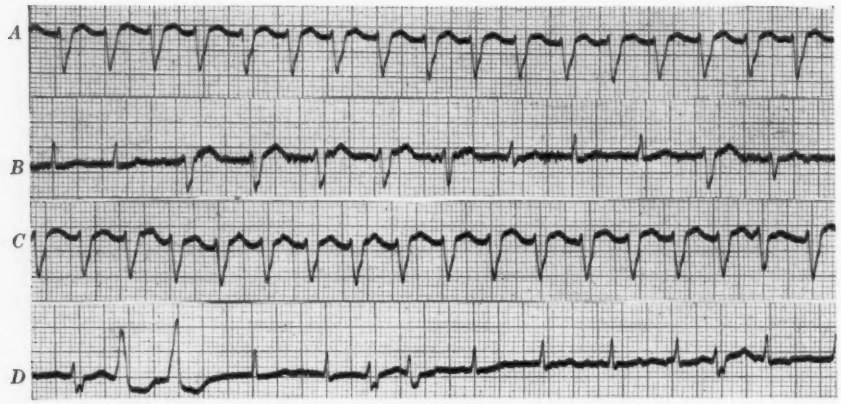

FIG. 5. Lead III. Ventricular tachycardia (*A*) disappears after eight minutes of hyperventilation and is replaced by multiple extrasystoles with a slower rate (*B*). Three minutes after the end of hyperventilation the original tachycardia recurred (*C*) and it disappeared after a second period of hyperventilation lasting nine minutes (*D*). Multiform extrasystoles appear.

the tachycardia and multiform ventricular extrasystoles were recorded (fig. 5*D*).

F. H., a 52 year-old patient, was admitted because of an acute posterolateral infarction of the left ventricle. On examination the patient had a sinus rhythm with multiple ventricular extrasystoles. These became permanent within a few days and the pattern as seen in the three standard leads in figure 6 was continuously present. The ventricular rate was approximately 100 beats per minute. Figure 7*A* (lead I) was recorded after five minutes of hyperventilation. Regular groups of seven ventricular extrasystoles had appeared coupled to a sinus beat. Following 12 minutes of hyperventilation (fig. 7*B*) three ventricular extrasystoles followed each sinus beat. Thus, the number of extrasystoles had diminished markedly. A few minutes after the end of hyperventilation the sinus beats again became infrequent. Five minutes after hyperventilation ended the number of extrasystoles after each sinus beat had increased to six (fig. 7*C*), and after an additional 10 minutes normal sinus beats had disappeared and there was a continuous chain of extrasystoles (fig. 7*D*).

E. M., a 27 year-old male, was admitted because of a duodenal ulcer. The control electrocardiogram revealed a ventricular tachycardia with a rate of 84 beats per minute (fig. 8*A* and *B*). Very few sinus beats with a rate of 75 appeared; usually there was only one sinus beat, rarely three were encountered (fig. 8*A*). The chains of ventricular extrasystoles were so long because most of them were reversely conducted to the auricle and disturbed impulse formation in the sinus node. When this retrograde conduction ceased the sinus beats appeared. Combination beats were often seen because of the

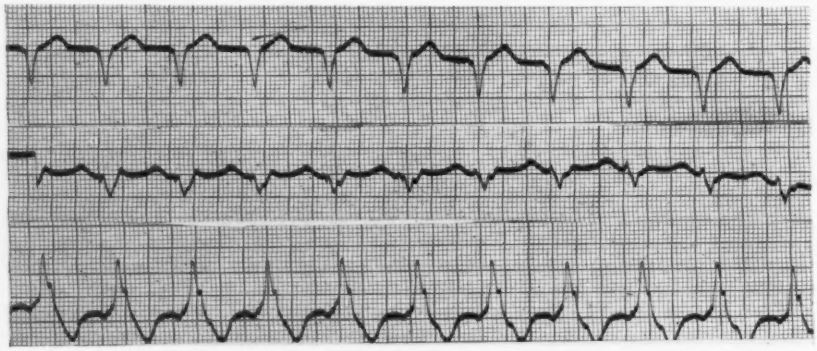

FIG. 6. Paroxysmal ventricular tachycardia in the three standard leads.

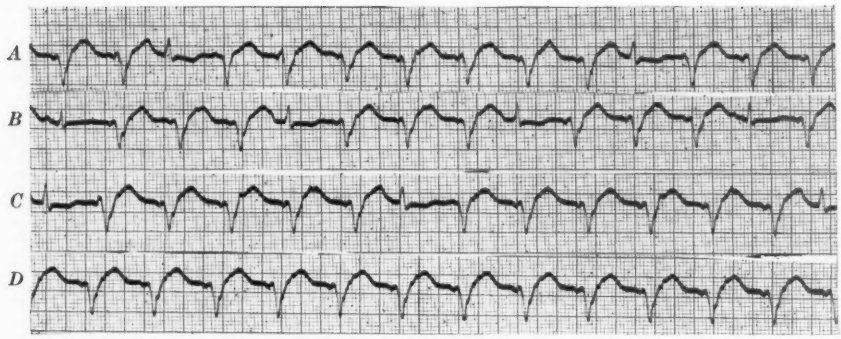

FIG. 7. (*A*) shows Lead I of the same patient shown in figure 6 after hyperventilation lasting five minutes and (*B*), after hyperventilation lasting 12 minutes. Here only three ventricular extrasystoles follow each normal beat. Five minutes after the end of the hyperventilation (*C*) the number of extrasystoles increased and after 10 more minutes (*D*) there was again an uninterrupted chain of extrasystoles.

simultaneous activation of a part of the ventricle by sinus impulse and ectopic impulse. Hyperventilation studies repeated 11 times in three weeks, always yielded the same results. In every experiment hyperventilation reestablished sinus rhythm within a few minutes. Figure 8*C* shows the continuous sinus rhythm four minutes after the beginning of hyperventilation and one minute after it had been discontinued. While the possibility exists that the sinus tachycardia at the end of hyperventilation prevented the appearance of the slow extrasystoles with long coupling, the tracing one minute after the end of hyperventilation (fig. 8*C*, second half) shows adequately long diastoles; therefore this explanation for the disappearance of the extrasystoles is unacceptable. Figure 8*D* shows the electrocardiogram six minutes after the end of hyperventilation with a sinus rhythm still persist-

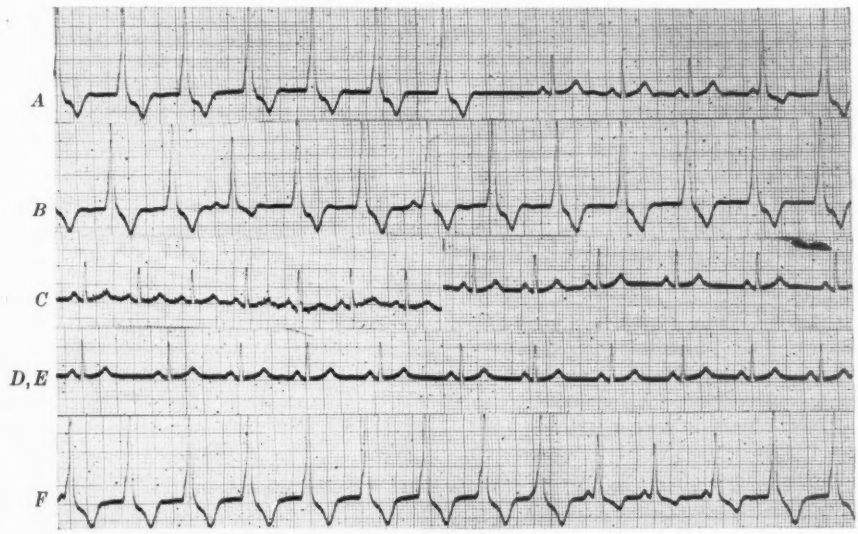

FIG. 8. Lead II. Attacks of ventricular tachycardia with only a few sinus beats between them (*A* and *B*). (*C*) shows a regular sinus rhythm after four minutes of hyperventilation; (*D*) taken one minute later shows still only sinus rhythm and so does the tracing in (*E*) obtained six minutes after the end of hyperventilation. The original arrhythmia had returned in (*F*) which was obtained shortly after (*E*).

ing. This was never observed in this patient without hyperventilation but always appeared as a consequence of it. A few seconds later figure 8*E* was recorded and showed the same pattern as the control electrocardiogram.

In one case of auricular fibrillation of several hours duration the fibrillation disappeared one minute after hyperventilation for eight minutes. It did not return until the patient was discharged three days later. A correlation between the hyperventilation and the disappearance of the fibrillation is not certain. In seven patients with auricular flutter hyperventilation was without effect.

Discussion

The mechanism of these profound effects of hyperventilation upon the arrhythmias presented is not known. Two possibilities immediately appear as plausible explanations, namely, exercise and alteration in acid-base balance. Since our subjects breathed at approximately normal respiratory rates with little effort and since the heart rate did not increase during hyperventilation, exercise with its attendant change in sympathetic tonus can be ruled out. Changes of the blood pressure during hyperventilation in man are minimal.[6, 8]

Marked alterations in acid-base balance and in serum electrolytes have been noted in acute hyperventilation studies,[1, 9] of which variations in serum potassium and pH are most likely to affect cardiac impulse formation. Changes in serum potassium are minimal and cannot readily be expected to play a role. We know little, however, about the changes within the myocardial cells. A striking transitory increase in the serum pH, occurring within two to three minutes after hyperventilation starts, persisting for approximately six minutes after it terminates and promptly returning to normal thereafter, has been substantiated in several studies.[2, 4] Thus it is possible that the mechanism involved, whatever it may be, depends upon alterations in the serum pH, since this change is significant and alterations in the form of arrhythmias are known to coincide with the change in pH. The importance of fluctuations in serum pH in the mechanism of the origin of extrasystoles, is well known, especially in regard to the effect on the supernormal phase of recovery.[7, 12] Since stimuli which are ordinarily subthreshold become effective or stimuli are formed during such periods of enhanced excitability, the supernormal phase has been assumed to have significance in the origin of extrasystoles, although it is not the sole factor involved. With these facts in mind, one can formulate the following tempting hypothesis. Voluntary overbreathing reduces alveolar carbon dioxide tension which, in turn, causes a reduction in the carbon dioxide tension of arterial blood and, consequently, an increase in the pH of arterial blood. This new pH lessens or abolishes the tendency to ectopic cardiac impulse formation by virtue of its effect on the supernormal recovery phase or through a change of the electrolyte balance. As a result the existing arrhythmia is either eliminated or markedly diminished. Upon cessation of overbreathing and rapid return of alveolar carbon dioxide tension and arterial pH to normal, the inhibition of ectopic impulse formation is released and the ectopic arrhythmia returns.

Extrasystoles initiated by aconitine disappear during asphyxia.[10] Experimental analysis shows that this effect is not due to anoxia but is the consequence of hypercapnia; breathing of a mixture of 20 per cent carbon dioxide and 80 per cent oxygen abolishes the extrasystoles temporarily. These results are interesting since the appearance of dangerous ectopic ventricular arrhythmias and of ventricular fibrillation recently has been reported to follow rapid reduction of an existing hypercapnia.[3, 14]

Summary

Instances of various arrhythmias which were temporarily diminished or abolished by voluntary overbreathing are presented.

The mechanism is unknown, but is believed to be the effect of increased pH of arterial blood upon the supernormal phase of recovery and perhaps changes of the electrolyte pattern.

Summario in Interlingua

Esseva studiate le influentia de hyperventilation super varie formas de arrhythmia cardiac. Esseva constatate que hyperventilation causa le disparition temporari de extrasystoles auricular e ventricular. Illo aboli tachycardias parox-

ysmal auricular e ventricular e accessos de breve fibrillation paroxysmal auricular.

Le mechanismo de iste effectos non es cognoscite, sed nos opina que illo involve un augmentate pH del sanguine arterial e possibilemente un cambiate configuration del electrolytos.

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Mitral Insufficiency: Cardiac Mechanics as Studied with the Kinetocardiogram and Ballistocardiogram

By William T. Tucker, M.D., John L. Knowles, M.S. and E. E. Eddleman, Jr., M.D.

Precordial movements (kinetocardiograms) and ballistocardiograms were studied in patients with "pure" mitral insufficiency. Certain characteristic features of the records were noted and contrasted with those found in patients with mitral stenosis. The finding suggests fundamental differences in the mode of ventricular contraction and relaxation in mitral insufficiency and mitral stenosis.

A PREVIOUS paper has defined precordial chest-wall movements (kinetocardiograms) in patients with mitral stenosis.[1] The present study was undertaken in an effort to ascertain the precordial chest-wall movements in patients with mitral insufficiency, and to compare these with the kinetocardiograms from patients with mitral stenosis.

Technics

Precordial chest-wall movements were obtained by methods previously described.[2] The apparatus consists of a bellows-air-conduction system connected to a piezoelectric transducer and recorded on a Sanborn Poly-viso four-channel recorder. A detailed analysis of the normal patterns obtained by such technics has been previously presented.[3, 4] Direct ballistocardiograms were taken simultaneously with patients on a sand or putty surface to minimize body oscillations.[5, 6] Electrocardiograms and carotid pulses were obtained simultaneously with the kinetocardiograms and ballistocardiograms. Kinetocardiograms were recorded from the precordium in the areas corresponding to the V leads of the electrocardiogram and are designated as KV_1, KV_2 etc.

Patients

The validity of such a study as this depends upon an accurate diagnosis of the cardiac valvular lesion. In order to evaluate the precordial movements, it seemed desirable to study first only patients in which the diagnosis of "pure" mitral insufficiency was reasonably certain.

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There is no uniformity as to what physical signs constitute the most reliable clinical evidence for mitral insufficiency. However, the following criteria appeared most reasonable and consistent with the findings presented by others for mitral insufficiency:[7, 8, 9, 10] (1) an apical systolic murmur transmitted to the axilla of grade III or more intensity, (2) absence of a diastolic murmur, (3) history of rheumatic fever, (4) no evidence of any other valvular involvement, (5) left ventricular predominance either by fluoroscopy or by the electrocardiogram, and (6) some clinical evidence of heart disease. Not all of these patients met all of the criteria above. However, 11 patients were selected in which the diagnosis appeared reasonably certain clinically, and in whom the majority of the above findings were noted. The essential clinical features of these patients are listed in table 1. Patient 8 had the presence of a grade I diastolic rumble at the apex and initially was considered to have mitral stenosis as well as mitral insufficiency. However, operation revealed only a large dilated mitral valve with insufficiency and no detectable stenosis. Although it was possible that there was still minimal mitral stenosis present in this patient, mitral insufficiency was certainly the major valvular lesion, and it was felt justifiable to include this patient in the study. Patient 10 did not have a history of rheumatic fever, but the apical murmur was loud and harsh and clinically consistent with the diagnosis of mitral insufficiency. He did have a minimal elevation of blood pressure, but it was not considered of sufficient degree to exclude this patient from the series. In addition, cardiac catheterization studies in this patient revealed no evidence of a congenital defect. Two of the patients (patients 4 and 5) had loud apical systolic murmurs which were musical in quality. Patients 1, 2, 3, 5 and 11 (table 1) had late systolic crescendo murmurs, while patients 8, 9 and 10 had murmurs which extended throughout systole. Figure 1 is an illustration of the phonocardiogram from patient 4 in whom there was a musical quality to the systolic murmur.

TABLE 1.—*Clinical Data on the 11 Patients Studied with "Pure" Mitral Insufficiency*

Patient	History of Rheumatic Fever	Systolic Apical Murmur		Third Heart Sound	Fluoroscopic Examination	Electrocardiogram		Functional Class	Miscellaneous
		Grade	Time in Systole			Mean QRS Axis	Left Ventricular Hypertrophy on ECG		
1	Yes	IV	Late	No	Minimal left ventricular enlargement	55°	No	I	Large pulsating left auricle
2	Yes	III	Mid and Late	No	Minimal L.V.E.	−5°	Yes	I	Enlarged left aur.
3	Yes	IV	Late	Yes	Minimal L.V.E.	−5°	Yes	I	No aur. enlargement
4	Yes	VI	Mid and Late	Yes	Moderate L.V.E.	60°	No	II	
5	Yes	III	Late	Yes	Minimal L.V.E.	5°	No	I	
6	No	IV	Mid and Late	No	Minimal L.V.E.	80°	No	I	
7	Yes	IV	Mid	Yes	Moderate L.V.E.	75°	No	I	Enlarged left aur.
8	Yes	III	Pan	No	Minimal L.V.E.	60°	Yes	III	Enlarged pulsating left aur. at operation
9	No	IV	Pan	No	Moderate L.V.E.	−20°	Yes	I	Large pulsating left aur.
10	No	III	Pan	No	Minimal L.V.E.	45°	Yes	II	No auricular enlargement
11	Yes	III	Mid and Late	No	Minimal L.V.E.	60°	Strain	I	

The functional class is based on the standards of the American Heart Association. L.V.E. indicates left ventricular enlargement. The grade of the murmur is according to the classification of Levine.

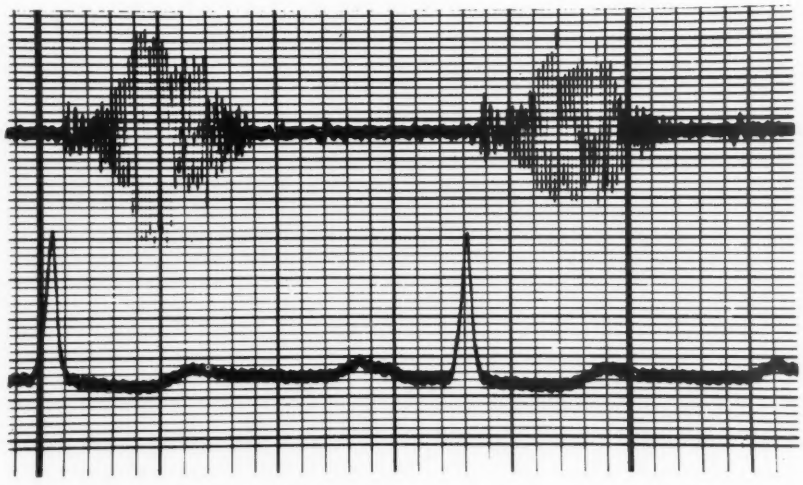

FIG. 1. The phonocardiogram taken from patient 4 with "pure" mitral insufficiency in which there was a musical quality to the murmur. Note the high-pitch vibrations occurring in midsystole which are of large amplitude.

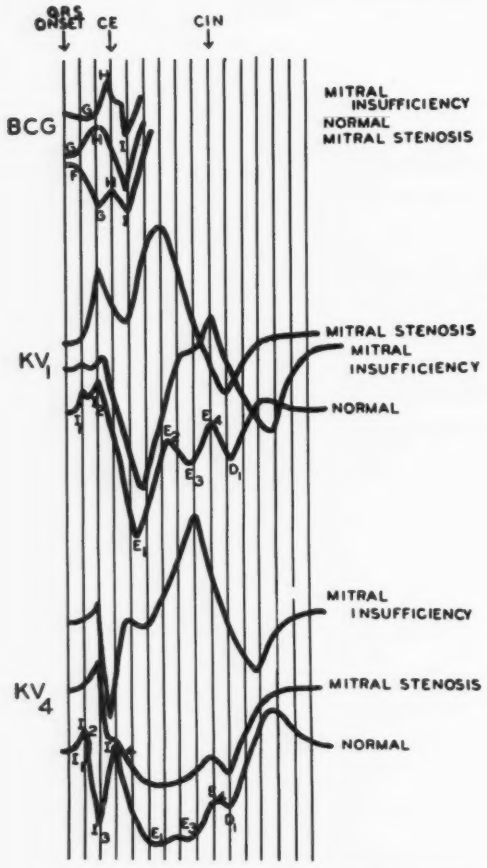

FIG. 2. Schematic drawing of the representative findings in patients with mitral insufficiency as compared with those with mitral stenosis and normal subjects. Only the initial portion of the ballistocardiogram is included in the top three traces showing the pre-ejection configuration of the ballistocardiogram as usually noted. The vertical lines represent .04 second. The onset of the QRS complex of the electrocardiogram is indicated by the first arrow at the top of the drawing. The upstroke of the carotid pulse is indicated by the next arrow and marked Ce (carotid ejection), and the carotid incisural notch (Cin) is indicated by the third arrow. The pattern for the normal kinetocardiogram is inserted and labelled; however, as there are certain time variations as well as configuration changes in the traces from patients with mitral insufficiency, the points are not labelled although many of the points are probably comparable.

KV_1 and KV_4 areas of the kinetocardiogram are presented, KV_2 and KV_3 are usually of an intermediate character to the two traces presented and, therefore, will not be discussed in detail. Note that the records taken from patients with mitral insufficiency are quite different from both the normal subject and the patient with mitral stenosis. In the KV_1 area, the trace taken from a patient with mitral stenosis differs more from that of a normal person, while the trace from the apical region (KV_4) differs more from the normal pattern in patients with mitral insufficiency. Note the late systolic outward movement in the region of the apex in patients with mitral insufficiency in contrast to the absence of this movement in a trace from normal persons and from a patient with mitral stenosis. The drawing is best understood by referring to the text in which the motions are broken down according to time periods from the onset of the QRS complex to carotid upstroke and from the carotid upstroke to the carotid incisural notch.

Note that the early footward movement in the ballistocardiogram from a patient with mitral stenosis is absent in the traces of a normal subject and of a patient with mitral insufficiency. Also note that in a patient with mitral stenosis there is a sharp footward movement .04 second after the onset of the QRS complex which is absent in patients with mitral insufficiency. The GH upstrokes in the ballistocardiograms are delayed in mitral stenosis and mitral insufficiency as compared with that in normal traces. Patients with mitral insufficiency again may have a definite notch in the HI downstroke as illustrated.

SIGNIFICANT FEATURES OF THE RECORDS FROM PATIENTS WITH "PURE" MITRAL INSUFFICIENCY

Figure 2 is a drawing of the typical findings of the kinetocardiograms in patients with mitral insufficiency. The typical findings from patients with mitral stenosis are included for contrast as well as those from normal subjects. Figure 3 is a representative tracing from patient 1. Figure 2 is best employed in following the subsequent discussion. It is obvious from figure 2 that the traces from subjects with mitral insufficiency are quite different from those taken from patients with mitral stenosis and from normal subjects. The differences from normal subjects will be presented first.

Traces From the Right Parasternal Region of the Chest (KV_1)

Period from the Onset of the QRS Complex to the Carotid Upstroke. Patients with mitral insufficiency usually have a double outward movement in the KV_1 area not too different in appearance from that of normal subjects. The onset of the initial outward movement which begins in normal subjects approximately .02 second after the onset of the QRS complex, when present in patients with mitral insufficiency, usually occurs in the normal time rela-

tionship. However, the peak of the second outward movement is usually delayed when compared with this finding in the normal subjects by approximately .02 to .04 second duration. The parasternal region then begins moving inward approximately .02 second before the onset of ejection as determined by the carotid upstroke.

Period from the Onset of the Carotid Upstroke to the Carotid Incisural Notch. As mentioned, the right parasternal region usually begins moving inward before the carotid upstroke. However, the main inward retraction of the parasternal region of the chest takes place during the early portion of ejection. The depth of this systolic retraction goes well below the baseline and is not dissimilar in time or configuration to that noted in normal subjects. It usually reaches its maximal retraction approximately .04 to .06 second after the I point in the ballistocardiogram or during the IJ upstroke. The chest then begins to move outward during the period of mid and late portion of ejection, going above the diastolic or initial resting level of the chest. The outward peak of this motion appears well after the J point in the ballistocardiogram and, therefore, does not correspond in time with the J point as does the midsystolic outward movement E_1-E_2 in normal subjects (fig. 2). The trace also shows a notch in late systole but continues to move outward up to or slightly after the time of the carotid incisural notch. *This point, which corresponds in time to the carotid incisural notch, was in all instances above the diastolic or resting level of the chest.*

Period of Diastole Beginning at the Carotid Incisural Notch: The parasternal region of the chest (KV_1) again moves inward, usually not to the same degree as that noted during the retraction of the chest during early ejection. However, it is a well-defined movement and its nadir occurs after the corresponding point in the normal trace (approximately .08 second). In one instance, it was as much as .20 second after the carotid incisural notch. At this time, the chest moves outward in a slow fashion, reaching the diastolic or resting level of the chest before the next onset of the QRS complex.

Apical Region of the Chest (KV_4)

Period from the Onset of the QRS Complex to the Carotid Upstroke. In most instances the apical region of the chest begins moving outward similarly to the movement in normal subjects, starting .02 second after the onset of the QRS complex. However, the peak of this outward motion is delayed .04 second as compared with the time of this movement in normal subjects. This is followed immediately by a very sharp retraction of the apical region of the chest before the onset of the carotid upstroke, the retraction reaching its nadir before the carotid upstroke begins. In some instances, this retraction of the apical region of the chest is most evident in the KV_3 region rather than in KV_4. It usually parallels the second outward movement in the parasternal region of the chest. Only one patient did not have an appreciable retraction during this period (patient 6). However, a well-defined inward

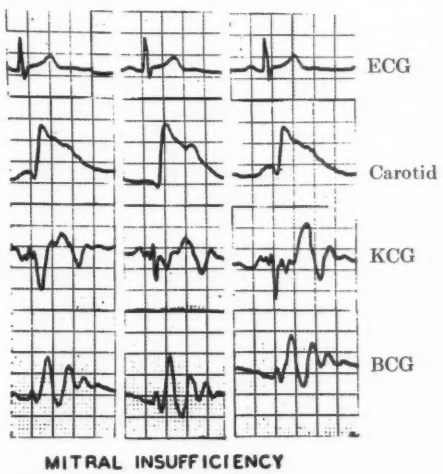

FIG. 3. Representative trace taken from a patient with mitral insufficiency. The left hand trace is that taken from the KV_1 area or the left parasternal region. The middle trace is that from the KV_3 area and the right hand trace is that taken from the KV_4 area. Again note the marked inward movement of the trace taken from the apical region before the onset of the carotid upstroke. There is only minimal retraction of the apex trace during systole and the chest is displaced outward above the diastolic or resting level of the chest during mid and late systole. This is followed immediately by a well-marked inward movement of the apical region of the chest.

notch was present, corresponding in time to that noted in the other patients. This retraction of the apical region of the chest is then followed by an outward movement which begins just before the upstroke of the carotid trace and continues on into ejection.

Period from the Carotid Upstroke to the Carotid Incisural Notch. As mentioned above, the outward movement of the apical region of the chest begins approximately .02 second before the upstroke of the carotid tracing and continues for approximately .02 to .04 second after the onset of the carotid upstroke, the peak being delayed as compared with the occurrence of this movement in normal subjects (fig. 2). At this time, in early ejection, there is in some instances a small inward motion of the chest, but never the systolic retraction of the chest seen in normal subjects (fig. 2). This inward movement during the early phase of ejection is of brief duration and immediately the apical region of the chest begins moving outward again at this time, going well above the diastolic or resting level of the chest. This outward motion usually reaches its peak before the carotid incisural notch by .04 to .08 second, at which time it begins moving inward. This late systolic anterior or outward movement of the chest is quite pronounced in all of the records, *displacing the chest wall out well above the diastolic or resting level of the chest.*

Period of Diastole Beginning with the Carotid Incisural Notch. The inward motion of the apical region of the chest, which begins shortly before the carotid incisural notch, is a well-marked movement. It terminates usually .12 second after the carotid incisural notch, following which there is a slow outward movement of the chest wall. This outward movement in the apical region precedes by .04 second the outward movement noted in the parasternal region of the chest (KV_1).

The records obtained from the KV_2 and KV_3 areas usually are of a transitional quality between those observed in the KV_4 and KV_1 areas. However, as some of the movements just described in the KV_4 area occasionally are more apparent in the KV_3 area, it is considered that for full evaluation of the traces, records must be taken from each position. In addition, there are noted in most instances small outward and inward movements following the onset of the P waves in the electrocardiogram which are presumed to be of auricular origin. However, these were not characteristic nor significantly altered from those noted in normal subjects, and therefore will not be discussed.

Ballistocardiograms in Patients with "Pure" Mitral Insufficiency

There were no consistent findings in the ballistocardiograms in these patients with mitral insufficiency. However, frequently alterations were noted in the initial portion of the ballistocardiogram which were different from those recorded in normal subjects and in patients with mitral stenosis (fig. 2). None of the patients with mitral insufficiency had a marked footward movement (FG downstroke) .04 second after the onset of the QRS complex, as was usually found in patients with mitral stenosis (fig. 2). The GH upstroke in most instances was delayed when compared with that of normal subjects and similar in time to that observed in patients with mitral stenosis. In three instances it was prominent and similar to that reported by Kuo and Schnabel.[11] The HI downstroke in most instances was notched in patients with mitral insufficiency, which is more marked than that observed in patients with mitral stenosis or in normal subjects. The diastolic portion of the ballistocardiogram in some instances was altered from that noted in normal subjects; however, there were no consistent features. Three of the patients had deep K points and large KL upstrokes (fig. 1). In others, this portion of the ballistocardiogram was not significantly altered.

Differences in Traces from Patients with Mitral Insufficiency from those of Mitral Stenosis

From figure 2, the differences in traces from patients with mitral stenosis and mitral insufficiency are quite striking. The following significant differences are noted:

(1) Patients with mitral stenosis have a marked outward movement of the precordium,

usually in the parasternal region, beginning .04 second after the onset of the QRS complex, while patients with mitral insufficiency have a normal or small outward motion .02 second after the onset of the QRS complex.

(2) Patients with mitral stenosis have an inward motion over the right parasternal area of the chest just preceding and during early ejection which rarely retracts below the diastolic level of the chest, in contrast to the well-defined and deep inward movement noted in patients with mitral insufficiency.

(3) Patients with mitral stenosis have a marked anterior displacement of the precordium usually during early and midsystole, in contrast to the marked anterior displacement of the precordium in late systole in patients with mitral insufficiency.

(4) During the ejection period, patients with mitral stenosis usually retract below the diastolic or resting level of the chest in the KV_4 area during the entire ejection phase, in contrast to a marked anterior and outward displacement of the precordium in patients with mitral insufficiency which becomes maximal before the time of the carotid incisural notch.

In summary, patients with mitral insufficiency lack the anterior swing of the heart which occurs .04 second after the onset of the QRS and which is considered to be due to the hypertrophied right ventricle of patients with mitral stenosis.[1] Patients with mitral insufficiency, instead of having an early or midsystolic anterior swing of the heart, apparently have a late systolic anterior swing of the heart lasting up to the time of the carotid incisural notch.

Studies of Patients with Combination of Mitral Stenosis and Mitral Insufficiency

Only preliminary observations can be made on the characteristics of the records of patients with both mitral stenosis and mitral insufficiency. Observations on eight patients who had, in addition to a well-defined diastolic rumble, a loud systolic apical murmur revealed a combination of the features described for both mitral stenosis and mitral insufficiency. Figure 4 is a record of a patient with both mitral stenosis and mitral insufficiency. Note the exaggerated anterior swing of the heart as well as the presence of a generalized precordial late-systolic anterior motion of the chest. From such limited observations it is uncertain at present whether the degree of the various lesions as reflected in the kinetocardiogram will represent a method of determining the predominance of either mitral stenosis or mitral insufficiency.

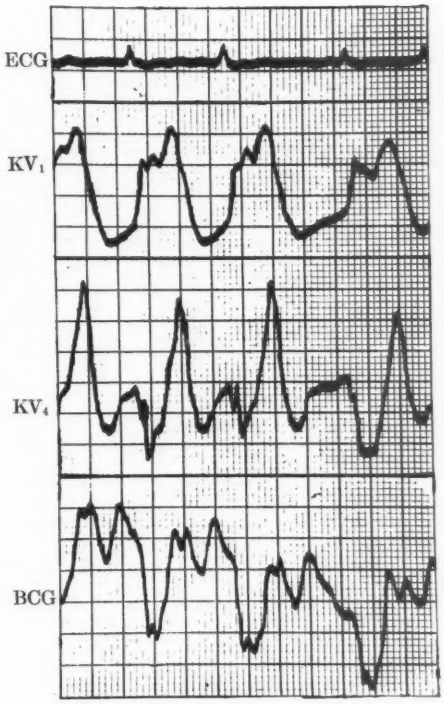

Fig. 4. Traces from a patient with both mitral stenosis and mitral insufficiency. Note that the records have certain characteristics of both lesions. There is an exaggerated anterior movement .04 second after the QRS complex in KV_1 like that found in mitral stenosis. In addition, there is a well-marked outward movement (KV_4) in late systole similar to that noted in "pure" mitral insufficiency. Preliminary observation suggests the kinetocardiograms may reflect the degree of valvular involvement; however, too few patients have been studied at present to be sure.

Comments

The variations in the precordial movements noted in patients with mitral insufficiency, from

both normal subjects and patients with mitral stenosis, suggest fundamental differences in the mode of contraction and relaxation of the ventricles. The mechanism for each of the movements is not at the present time clearly understood; however, there are certain features which were observed and which may be pointed out. The initial pre-ejection period, as observed in patients with mitral insufficiency, was not too different from that of normal persons, and lacked the marked outward movement in early systole found in patients with mitral stenosis (fig. 2). There was a slight delay in onset of the initial outward movement of the entire precordium and the subsequent retraction in the region of the apex (fig. 2). The delay in onset of the retraction may possibly be due to a late arrival of the excitation wave as a result of ventricular hypertrophy or an increase in the electromechanical lag. The retraction was exaggerated in amplitude over normal in all but one instance, in which it was represented only by an inward notch. This patient had the largest heart of any one of the series and the poorest functional capacity. Thus it is possible that the retraction of the apex was absent because of changes in the contraction process as a result of ventricular dilatation. The exaggeration of the apical retraction may be explained as being the result of a more forceful shortening process of the heart. Why this should occur is not apparent at this time.

The late systolic outward or anterior movement of the precordium is one of the most significant features in the records obtained from patients with mitral insufficiency (fig. 2). At the present time there is no objective evidence as to the actual mechanism of this late outward systolic movement of the precordium, but its presence from the apical region to the KV_1 site suggests that it is due to an anterior movement of the heart at this time. A possible mechanism may be that of an anterior displacement of the heart as a result of auricular enlargement by the blood being ejected posteriorly and headward through the insufficient mitral valve during systole. The left auricular pressure curves in mitral insufficiency as well as piezoesophagraphic observations and electrokymographic traces from the left auricular border are compatible with this hypothesis in that they all demonstrate an outward movement in systole, the movement being greater just before the end of ejection.[10, 12, 13, 14] In addition, the work of Wiggers has shown that regurgitation of blood from the ventricles into the auricles probably takes place during late systole and even into the isometric relaxation phase.[15] The late systolic murmur correlates well with this outward movement of the precordium and the time of regurgitation; however, it was present even in those patients with early systolic murmur. Other factors in the genesis of the movement, such as elongation and inflow tract relaxation, have not been excluded.

It is likely that these changes in the precordial movements occur only after some cardiac impairment has taken place. This is exemplified by two patients not included in this series who had grade I to II systolic apical murmurs and a definite history of rheumatic fever. Even though the murmurs were faint and not comparable with those of the patients presented in this study, there was apparently organic mitral insufficiency. Neither of these two patients had fluoroscopic, clinical or electrocardiographic evidence of any functional impairment or enlargement of the heart. Thus alterations in the kinetocardiographic patterns probably depend upon the development of alterations in the contractile processes, and, therefore, minimal lesions do not change the precordial movements. Early and small degrees of mitral insufficiency probably cannot be recognized by kinetocardiographic traces. Thus differential diagnosis between functional and organic murmurs in early stages can probably not be made. This, in itself, does not necessarily limit the potential value of the kinetocardiographic tracings in that it may offer a means to recognize early ventricular functional impairment in mitral insufficiency.

In contrast to the rather consistent findings in the kinetocardiograms of patients with mitral insufficiency, the ballistocardiograms do not appear to be consistent. The pre-ejection portion was more reliable than the diastolic portion. However, exceptions to the pattern and configuration of this early portion of the

ballistocardiogram were encountered. Again caution must be used in interpreting the precordial movements in patients with combined mitral insufficiency and mitral stenosis until a sufficient number of patients have been studied in whom accurate evaluation of the degree of mitral insufficiency and mitral stenosis has been made.

Summary and Conclusions

(1) Eleven patients with presumably "pure" mitral insufficiency were studied by the ballistocardiographic and kinetocardiographic technics.

(2) Certain characteristics of the motions were noted: (a) An exaggerated early systolic retraction in the left precordium. (b) A marked anterior movement of the entire precordium during mid and late systole reaching a peak approximately at the time of the carotid incisural notch.

(3) It is pointed out that records of patients with mitral insufficiency differ from those of patients with mitral stenosis. However, it is uncertain at the present time, whether the kinetocardiogram can furnish an accurate guide to the relative degree of each.

Summario in Interlingua

(1) Esseva studiate per medio de technicas ballistocardiographic e cinetocardiographic 11 patientes con insufficientia mitral de forma presumitemente "pur."

(2) Certe characteristicas del motion esseva notate: (a) Un exaggerate retraction in le precordio sinistre al initio del systole. (b) Un marcate movimento del integre precordio verso le anterior durante le phases medie e final de systole. Iste movimento esseva maximal approximativemente al tempore del incisura carotide.

(3) Nos signala que registrationes ab patientes con insufficientia mitral differe ab illos obtenite ab patientes con stenosis mitral. Sed a iste tempore il non es certe que le cinetocardiogramma pote revelar le grado relative de o insufficientia o stenosis mitral.

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A Study of the Spatial Vectorcardiogram in Normal Subjects over the Age of Forty Years

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The spatial vectorcardiograms of 114 normal subjects over the age of 40 years have been studied. Differences in the form, orientation and magnitude of the QRS loops of these records and those of younger normal subjects recorded with the same techniques were found. The study represents a further step in defining the normal spatial vectorcardiograms.

In a previous study of the normal spatial vectorcardiogram recorded with the equilateral tetrahedral system of electrode placement, two basic forms of the QRS loop were recognized.[1] For descriptive purposes these were designated "types 1" and "2". "Type 1" QRS loops had smooth elliptoid spatial outlines, while "type 2" loops had more nearly circular outlines in space and were characterized by relatively large terminal areas behind the isoelectric point. The majority (88 per cent) of the records studied had "type 1" QRS loops and all of the remaining 12 per cent had "type 2" QRS loops. This classification into only two groups was based on the contour of the loops as visualized in three dimensions, and was not easily evident from plane projections of the vectorcardiogram or from scalar electrocardiograms, since both types of loops were found to vary widely in orientation. These findings were based on study of the records of 75 young adults ranging in age from 22 to 33 years. Differences between these records and those of subjects in other age groups are to be expected since the electrocardiogram is known to vary with age. The present study of the spatial vectorcardiogram in an older age group was undertaken as a further step in defining the normal spatial vectorcardiogram.

Materials and Methods

Studies were made on 91 males and 23 females ranging in age from 40 to 73 years. The mean age of the subjects studied was 45 years. The medical history and physical examination were negative for cardiovascular disease in all subjects. A teleoroentgenogram of the chest was obtained on each subject and showed no evidence of cardiac enlargement or pulmonary disease. All subjects had normal routine electrocardiograms.

Spatial vectorcardiograms were recorded, using the equilateral tetrahedral system of electrode placement. Frontal and left sagittal plane views were recorded simultaneously from two cathode ray oscilloscopes and the superior plane view and a stereoscopic view from the front, recorded by the method of Cronvich and his co-workers,[2] were obtained on each subject. Appropriate standardizing factors for the equilateral tetrahedron reference system were employed.[3] Each view of the vectorcardiogram was recorded at a variety of amplifications. Time was indicated in the records by interrupting the oscilloscopic trace 400 times per second and the direction of the trace was indicated by producing a comet shape of the segments of the trace with the blunt end of the segment in the lead.

Electrocardiograms, including the standard limb leads, unipolar limb leads, and precordial leads V_1 through V_6, were obtained on all subjects within a few minutes of the time the vectorcardiograms were recorded. In addition, the scalar components of the frontal and left sagittal plane projections of the vectorcardiogram, namely lead I, and unipolar leads from the left leg and the point on the back representing one of the apices of the tetrahedron, were recorded simultaneously using film speeds of 25 and 100 mm. per second.

The form, spatial orientation, and direction of inscription of the QRS components of the vectorcardiograms were observed in the plane projections and in the stereoscopic views. Similar observations on the form and spatial orientation of the P loops and T loops were made. Measurements of the magnitude and direction of the maximal vector of the QRS and T loops were made and were compared with those measurements from the records of younger normal subjects previously published.[1]

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Results

P Loop

Present recording methods make detailed information concerning the P loop difficult to obtain. Certain general features concerning the form and orientation of the P loops in this series of records were apparent however. The most common form of this loop encountered was a narrow elliptoid figure and, less commonly, a more nearly circular form usually containing one or more large indentations. The general orientation of the loops was such that the maximal vector was usually directed downward and to the left in the frontal plane projection, and vertically in the sagittal plane projection.

QRS Loops

Form. QRS loops with the contours previously designated types 1 and 2 were both represented in this series. In contrast to the records of younger normal subjects, however, there was not a clear-cut division into these two groups. Only 66 (58 per cent) of the QRS loops in this series had the definite characteristics of "type 1" loops in contrast to 88 per cent of the loops of younger subjects. There were no apparent differences in form of the "type 1" records in this series and those of younger subjects. Like those of younger subjects these loops had elliptoid contours with widths less than one-third of their respective lengths. They had smooth contours in three dimensions, although variations in orientation of different portions of the loops sometimes gave the illusion of irregularities in the plane projections. Figure 1 shows the frontal, left sagittal and frontal stereoscopic views of a record with a typical "type 1" QRS loop.

The remaining 49 records (42 per cent) had QRS loops of a more variable form. Some had the roughly circular spatial outline and large enclosed terminal area behind the isoelectric point which was characteristic of the loops labeled "type 2" in younger subjects. There was, however, no sharp division between these records and others which had somewhat circular outlines and enclosed terminal areas of variable size behind the isoelectric point. An example of the latter variety of QRS loop is shown in figure 2 and a typical "type 2" QRS loop is shown in figure 3.

Orientation and Magnitude. The magnitude and direction of the maximal QRS vectors in the frontal and the left sagittal plane are shown in figure 4. In this figure the mean value for this series of records is shown as a large solid dot, and the mean value of these measurements in the published series of records from younger normals is shown as an open circle. Since there was not a sharp division of QRS loops in this series into "types 1" and "2", the measurements of all loops are shown in this figure and in figure 5, and the average values shown for the records of younger subjects include both "types 1" and "2 loops". It is recognized that measurements of a single vector have limited meaning, however, some of the differences between the present series of records and those of younger subjects are

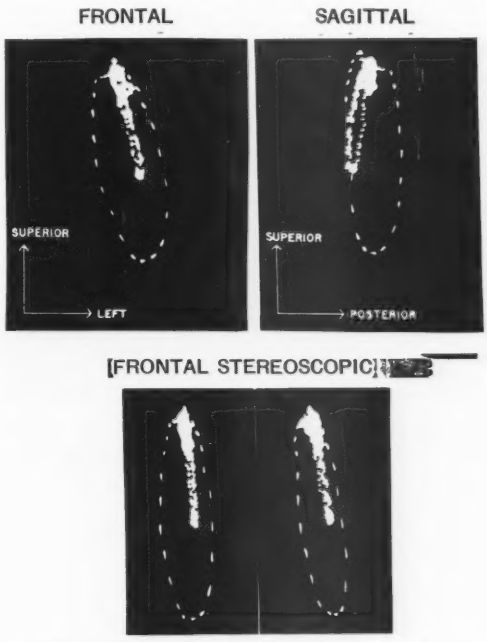

Fig. 1. Frontal, left sagittal and frontal stereoscopic views of a normal spatial vectorcardiogram with a "type 1" QRS loop. In this and the subsequent stereoscopic views, stereoscopic effects are best obtained by placing a card between the two photographs and viewing from a distance of 5 to 10 inches.

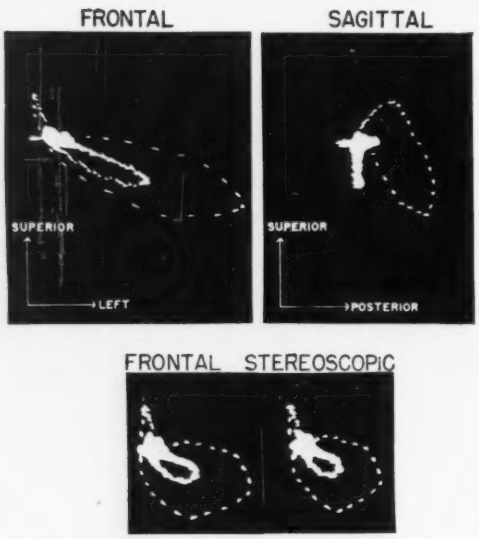

FIG. 2. Frontal, left sagittal and frontal stereoscopic views of a normal spatial vectorcardiogram with a QRS loop which is intermediate in form between characteristic "type 1" and "type 2" QRS loops.

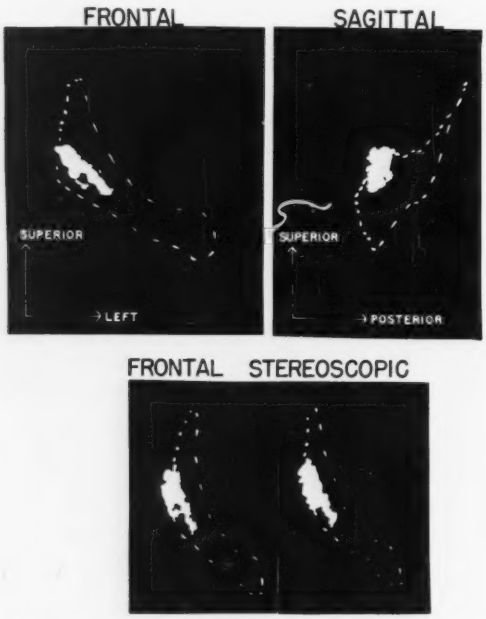

FIG. 3. Frontal, left sagittal and frontal stereoscopic views of a normal spatial vectorcardiogram with a "type 2" QRS loop.

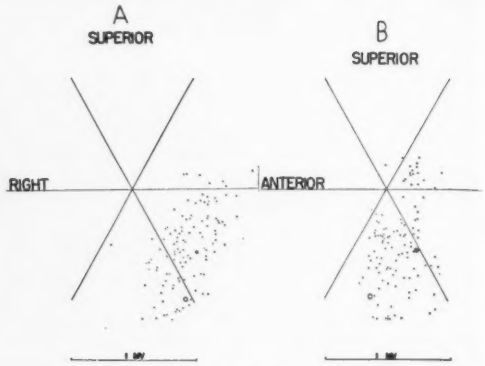

FIG. 4. Location of the termini of the maximal QRS vectors in the frontal and left sagittal planes. In this and the subsequent figures the average value of these measurements is shown as a large solid dot, and the average value of the maximal vector of younger normal subjects is shown as an open circle.

reflected in these measurements. As shown in figure 4, the average maximal QRS vector of this group of records was directed further to the left and posteriorly than that of younger subjects. The average maximal vector for this series was located at +44 degrees in a triaxial reference system in the frontal plane, and +63 degrees in a similar reference system applied to the left sagittal plane with the ±180 degrees axis located anteriorly. The average values in the series of records from younger normal subjects were +64 degrees in the frontal and +98 degrees in the left sagittal plane.

The magnitude of the average maximal QRS vector in both frontal and sagittal projections was less in this series than in that

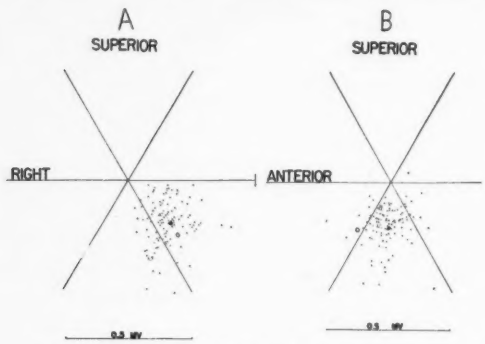

FIG. 5. Location of the termini of the maximal T vectors in the frontal and left sagittal planes.

TABLE 1.—*Summary of Measurements in Present Series and in a Series of Younger Subjects*

Age Group of Subjects	Maximal Vector QRS				Maximal Vector of T			
	Length (mv.)		Direction		Length (mv.)		Direction	
	Frontal	Sagittal	Frontal	Sagittal	Frontal	Sagittal	Frontal	Sagittal
Age 40 to 73 yrs.....	0.70	0.52	+43	+63	0.23	0.17	+43	+93
Age 22 to 33 yrs.....	0.95	0.83	+64	+98	0.28	0.23	+46	+124

from younger subjects. In this series the average maximal QRS vector in the frontal plane was 0.70 mv. compared with 0.95 mv. in the younger subjects, and 0.52 mv. in the sagittal plane in this series, compared with 0.83 mv. in the series of younger subjects. A summary of the measurements of maximal vectors in this series and in the series of younger subjects is presented in table 1.

In addition to the differences in orientation about the anteroposterior and transverse axes, which are reflected in the measurements of maximal QRS vectors, the records in this series differed from those of younger subjects in their average orientation about the longitudinal axis. Although all of the wide variations in orientation about this axis reported for younger subjects were encountered in this series, counterclockwise rotation about this axis, as viewed from the terminus of the maximal vector, was more frequently found in these records. This resulted in a larger number of QRS loops in the frontal plane projections being inscribed in a counterclockwise direction, while the direction of inscription in the sagittal plane remained unchanged. In this series 31 QRS loops were inscribed in a counterclockwise direction and 5 formed figures of 8 in the frontal plane. In the sagittal plane 100 were inscribed in a counterclockwise and 5 in a clockwise direction, while 9 formed figures of 8.

T Loops

In contrast to the differences in form, orientation and magnitude of the QRS loops in these records compared with those of young subjects, only one definite difference in the T loops was found. This consisted of a greater range in orientation about the transverse axis, with the T loop of average orientation directed further posteriorly than that of younger subjects. The orientation about the anteroposterior axis and the magnitude of the loops in both frontal and sagittal projections were similar to those of younger subjects. These characteristics are reflected in the measurements of the maximal T vectors shown in figure 5. The average of these vectors is shown as a large solid dot and has a magnitude of 0.23 mv. and a direction of +43 degrees in the frontal plane and a magnitude of 0.17 mv. and a direction of +93 degrees in the sagittal plane. The average values from the published series of records on younger normal subjects are shown as open circles and have a magnitude of 0.28 mv. and a direction of +46 degrees in the frontal plane and a magnitude of 0.23 mv. and a direction of +124 degrees in the sagittal plane. Variations in orientation of the T loops about their longitudinal axes were similar to those described in the records of younger subjects. The most common form of the T loops was a narrow elliptoid figure, but there was a range of form extending to almost circular figures.

DISCUSSION

It is well known that normal electrocardiograms may vary considerably. Studies of the spatial vectorcardiogram have suggested that this wide range in form of the normal electrocardiogram is mainly the result of variation in spatial orientation of electric forces produced in the heart, and that considerably less variation in the form of the normal spatial vectorcardiogram exists. This finding appears to offer promise that the spatial vectorcardiogram may allow a simpler and perhaps more certain method of recognizing normal electric phenomena from the heart and provides a founda-

tion for study of the abnormal vectorcardiogram.

In the age group between 22 and 33 years two patterns of the normal QRS loop recorded with the equilateral tetrahedral reference system were reported.[1] Later studies of the vectorcardiogram during and after pregnancy suggested that the position of the heart and extracardiac tissues were important factors in determining the configuration of the two types of normal QRS loops.[4] The probability that two basic variations in the order of excitation of the ventricles existed appeared unlikely from these studies since some of the loops with a "type 2" configuration during pregnancy changed to a "type 1" during deep inspiration and following delivery. In the present study although both the QRS loop configurations reported in younger subjects were found, there was not a sharp division into two groups and transitional forms between the two types were common. In addition to differences in the average form of QRS loops in this series and those of younger subjects, differences in orientation and magnitude were encountered. The average QRS loop in this series was smaller and was directed further to the left and posteriorly than that of younger subjects. It is not possible to define the exact mechanism of the differences in form, magnitude and orientation of these records and those of younger subjects. Differences in the position of the heart and extra cardiac tissues and/or differences in the electrical properties of the extra cardiac tissues appear to be the most likely possibilities, but actual differences in the process of ventricular depolarization cannot be excluded from these observations. It is of interest that the T loops of these subjects differed less from those of younger subjects than did the QRS loops.

Summary

The spatial vectorcardiograms recorded with the equilateral tetrahedral reference system of 114 normal subjects in the age range of 40 to 73 years have been studied. Differences in the orientation magnitude and form of the QRS loops of these records and those of younger subjects were found. The average QRS loop in this series was smaller and was oriented further to the left around the anteroposterior axis and further posteriorly around the transverse axis. Both of the QRS patterns previously reported in records of younger normal subjects recorded with this method of electrode placement were found but there was not a sharp division into these two groups. The form, orientation and magnitude of the T loops varied less from those of younger normal subjects than did the QRS loops.

Summario in Interlingua

Esseva studiate le vectocardiogramma spatial, registrate per medio del equilatere systema tetrahedral, de 114 subjectos normal de etates de inter 40 e 73 annos. Esseva constatate differentias inter iste registrationes e illos de plus juvene subjectos in le magnitude orientational e le forma del spira de QRS. Le spira median de QRS in iste serie esseva plus parve; illo esseva orientate plus verso le sinistra circa le axe anteroposterior e plus verso le posterior circa le axe transverse. Le duo configurationes de QRS, le quales esseva previemente reportate como characteristic occurrentias in vectocardiogrammas obtenite ab plus juvene subjectos normal per medio de iste methodo de placiamento del electrodos, occurreva etiam in le presente serie, sed illos non constitueva duo clarmente distincte gruppos. In comparation con le spiras de QRS, le forma, orientation, e magnitude del spiras de T deviava minus marcatemente ab illos de plus juvene subjectos normal.

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CLINICAL PROGRESS

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The Clinical Use of Digitalis Preparations

By CALVIN F. KAY, M.D.

NOTE: *In view of the length of this article, it is published in two issues. This issue will contain parts V through IX. The first part, I through IV was published in July, 1955.*—ED.

V. The Indications and Contraindications for Digitalis

Congestive Heart Failure

The prime indication for digitalis therapy is congestive heart failure resulting from defective myocardial contraction or from the inefficiency of excessive ventricular rate, or from a combination of the two. When congestive failure develops despite normal myocardial function (e.g. cardiac tamponade), digitalis is usually useless and may even be harmful. When the congestive failure is the result of a combination of mechanical factors (e.g. valvular stenosis) and of myocardial factors, (e.g. the dilation and/or hypertrophy that is the invariable result of functionally significant valvular disease), the degree of effectiveness of digitalis varies and is difficult to predict. Even when the fault lies entirely in the myocardium, digitalis may be ineffective, especially in acute inflammatory and degenerative diseases of the heart muscle (e.g. acute rheumatic fever, diphtheritic myocarditis, typhus). However, as a rule, if the heart is enlarged and congestive phenomena are present, digitalis should be used and will be beneficial.

Heart Disorders with Rapid Ventricular Rate

Digitalis is valuable in the management of most disorders of cardiac mechanism that are characterized by a rapid ventricular rate. When heart failure is present the results are more consistent than when it is not.

(1) *Chronic atrial fibrillation* with rapid ventricular rate is a classic indication for

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digitalis. Atrioventricular transmission of impulses is depressed with resulting ventricular slowing. The ventricular rate serves as a useful guide to the adequacy of digitalis if the important limitations of this index are not overlooked. Inadequate digitalization may be associated with adequate slowing at rest. If the rate rises sharply with slight exertion, the drug effect is predominantly neurogenic, and further benefits may be expected with higher dosage. If the optimal level of digitalization has been exceeded, ventricular slowing may be excessive, or the rate may again rise. The latter important manifestation of toxicity may be caused by ventricular premature beats, or by a regularization of the ventricular response with progressive tachycardia.[16]

When heart failure occurs in the presence of chronic atrial fibrillation at a slow ventricular rate, digitalization rarely results in dangerous depression of the rate at dosage levels that are effective in relief of the heart failure. The drug should be given cautiously and the effects followed closely.

(2) *Paroxysmal atrial fibrillation* is also an indication for digitalis therapy, but results are much less consistent than in chronic atrial fibrillation. When atrial fibrillation with rapid ventricular rate develops under stress (e.g., postoperatively, with acute febrile illness, and with pneumothorax) in an individual with little or no antecedent heart disease, digitalis in any form may be entirely ineffective, even at toxic levels. In a reported series,[63] neither reversion nor appreciable ventricular slowing followed intravenous preparations in 26 of 27 cases, or followed oral digoxin in 17 of 18 cases. The experience of many others has been much more favorable. Although negative results of digitalis therapy have often been observed, conversion to normal sinus rhythm has occurred many times, and an appreciable slowing of ventricular rate has been a frequent if not a consistent occurrence.

Continuous digitalization of a patient with recurring bouts of paroxysmal atrial fibrillation is not notably successful. The hope that attacks, when they occur, will be relatively asymptomatic, with a slow ventricular rate, is not realized in many individuals in whom paroxysms occur as frequently as before, and as severely. Since, in other patients, either the frequency or severity of the attacks is reduced, a trial of digitalis is warranted if other measures fail. The therapeutic limitations of digitalis in atrial fibrillation, acute or chronic, that is associated with thyrotoxicosis will be discussed.

(3) *In atrial flutter*, digitalis is usually of value. A rapid ventricular rate may be reduced by decreasing the ratio of ventricular to atrial beats, or the flutter may be converted to atrial fibrillation with a more readily controlled ventricular rate. To achieve either of these results, unusually large doses of digitalis are often required.[58] Sometimes fibrillation reverts to normal rhythm after the digitalis has been discontinued, especially with the assistance of quinidine. At other times sustained digitalis therapy is indicated.

(4) *Paroxysmal atrial tachycardia* usually responds to simple measures and rarely requires digitalis. If the attack is protracted, especially if a serious form of heart disease is present, or if the signs of heart failure are developing, digitalis is the drug of choice. Abrupt reversion to sinus rhythm frequently results. Avoid, of course, the serious mistake of giving digitalis to a patient with paroxysmal atrial tachycardia induced by digitalis toxicity.

(5) *Paroxysmal ventricular tachycardia* should always suggest the possibility of digitalis intoxication. Even when this can be excluded with certainty, other measures should be exhaustively tried before digitalis is used.

(6) *Ventricular premature beats*, unless caused by digitalis toxicity, are not a contraindication to its use. This form of arrhythmia may be a manifestation of stress in a failing heart. Relief of the failure with the help of digitalis may result in the disappearance of the premature beats.

(7) *Sinus tachycardia* is neither an indication nor a contraindication to digitalis therapy. A slight slowing of heart rate often accompanies restoration of compensation but it is not a useful guide to the adequacy of digitalization.

When sinus tachycardia is caused by anything other than heart failure, the heart rate will be little influenced by digitalis unless toxic doses are used and then it may be increased.

Heart Block

In persistent complete heart block with failure, digitalis is indicated. The hazard of digitalis administration to a patient with partial or intermittent heart block has been overemphasized, but cannot be ignored. Divergent opinions are cited by Blumgart and Altschule[64] who demonstrated, in 19 such patients with arteriosclerotic and rheumatic heart disease, that the effects of drug and disease upon atrioventricular conduction were not additive. The pre-existing abnormal conduction was not appreciably disturbed by therapeutically effective doses of digitalis. However, attempts to convert intermittent atrioventricular block with syncopal seizures to permanent complete heart block have been occasionally successful. Digitalis is likely to increase the frequency of syncopal seizures associated with carotid sinus sensitivity.[65]

Acute Myocardial Infarction and Angina Pectoris

Opinions differ concerning the use of digitalis after acute myocardial infarction. Some believe that it should be used almost routinely; others recommend it only as a last resort in advanced failure, fearing the drug induction of a fatal arrhythmia or cardiac rupture. Evidence from coronary occlusion experiments upon animals indicates a hazard in its use.[66] In a controlled human study,[67] no evidence of hazard was demonstrated. Most patients with acute infarction do not need digitalis when other measures are appropriately used to prevent the development of congestive failure. If, despite these, progressive failure is evident, cautious digitalis administration is indicated. Rapid digitalization or dosages approaching a toxic level should be avoided. The symptoms of angina pectoris are not significantly influenced by digitalis.[68] It is neither an indication for the drug, nor a contraindication if heart failure is present.

Disorders Not Primarily of Cardiac Origin

A variety of disorders may cause symptoms and findings similar in one or many ways to those caused by heart disease. *Dyspnea* and *palpitation* are the outstanding symptoms of one group of these disorders, which include anemia, thyrotoxicosis, arteriovenous fistula, beri beri, Paget's disease, neurocirculatory asthenia, pregnancy, and advanced pulmonary disease. In these conditions the cardiac output is characteristically high. *Edema* is the outstanding feature of another group, which includes hypoproteinemic states, myxedema, acute glomerulonephritis, and toxemia of pregnancy. Most of these disorders increase the work of the heart. An intrinsically diseased heart, capable of adequate function for normal demands, may fail under the added stress. For example, if a patient with well compensated mitral stenosis becomes pregnant, congestive heart failure may develop, and a need for digitalis is created. Some of these disorders, if sufficiently severe or protracted, may be the direct cause of intrinsic heart disease.

In general, in the disorders not primarily of cardiac origin, digitalis will not help unless the heart muscle is failing. Specifically, the indications for and against, and the effects of, digitalis may be considered:

(1) In acute nephritis and in toxemia of pregnancy, cardiac dilatation occurs under the stress of the associated hypervolemia, hypertension and capillary vascular disturbances in the myocardium. When hypertension, elevated venous pressure, and cardiac enlargement are all present, digitalis is often useful.

(2) In anemia, some cardiac enlargement may be expected with hemoglobin levels at or below 40 per cent of normal. With sustained very severe anemias, the pathogenic sequence is dilatation, hypertrophy, myocardial atrophy, and lipoid replacement.[69] Even if frank manifestations of congestive failure occur, digitalis preparations are rarely helpful in anemic heart disease.

(3) In myxedema, the cardiac silhouette may be greatly enlarged, often from pericardial effusion, and many of the physical

findings usually associated with congestive failure may be present. If digitalis is effective, it is in meeting the demands of associated intrinsic heart disease of other etiology, for digitalis is not useful in uncomplicated myxedema.

(4) In beri beri, specific vitamin and general nutritional therapy is ordinarily highly effective. Digitalis may later be of some help if cardiac enlargement and elevated venous pressure persist, as occasionally they do.

(5) Thyrotoxicosis is especially prone to exaggerate the effects of coincident heart disease of other etiology. Although thyrotoxicosis produces no specific pathologic lesions, it alters cardiac metabolism. Atrial fibrillation frequently develops, and when it does, the ventricular rate is usually rapid. When heart failure occurs, all measures usually effective, including digitalis, should be employed. However, the results may be disappointing until the thyrotoxicity is controlled. With atrial fibrillation, large doses of digitalis are usually required to produce an appreciable slowing of ventricular rate. No attempt should be made to reduce the rate below that which would be present if the patient were in normal sinus rhythm.

(6) Advanced pulmonary disease may be associated with a variety of physiologic and anatomic abnormalities of the heart and general circulation.[70] Digoxin[70] or lanatoside C[71] may result in an acute rise in cardiac output, even when it had been above normal before medication. Oxygen saturation may concurrently fall. In a longer term study, digitalis appeared to be a factor in clinical improvement, associated with a fall in pulmonary arterial pressure and in cardiac output.[70] Digitalization has been suspected as a cause of sudden death in these individuals,[71] but a cautious trial of the drug is indicated in patients with severe dyspnea, cyanosis, appreciable cardiac enlargement, or peripheral evidences of congestive failure. The results may be good, bad, or indifferent.

Potential Heart Failure

Also, opinions differ concerning the value of giving digitalis to the patient with a large heart, but in whom failure has never appeared. In these individuals, as in normal people, resting cardiac output is either little changed or reduced by digitalis administration.[34] The concept of "prophylactic digitalization" was recommended by Christian[72] a generation ago. It is supported by some evidence in man[73] and in animals,[21] but has never gained wide acceptance. Szent-Gyorgyi,[21] impressed with the validity of the concept, concludes: "Why give the heart rope to hang itself?" This important problem warrants further attention. It may be that a patient with progressive cardiac enlargement deserves digitalis whether failure is present or not.

VI. The Administration of Digitalis

When it has been decided that a digitalis preparation should be given, the usual plan calls for selection of a suitable drug and its administration in amounts sufficient to produce a minimum effective level of digitalization within a reasonable time. The dosage is then adjusted to reach an optimum level, and finally readjusted to maintain the optimum level for a long period of time. Since any plan of therapy requires a considered guess at the amount of drug required to produce a desired effect, it is the first responsibility of the physician to recognize, as well as possible, those patients in whom major toxicity may result from doses that would ordinarily be safe. Cautious administration is necessary in the aged or debilitated, in patients with myxedema, electrolyte disturbances, advanced pulmonary disease, recent myocardial infarction or active myocarditis, and it is particularly necessary in those who have already received digitalis in any form.

Responsibility for establishing with certainty whether or not the patient is already digitalized is too often neglected, especially when a patient is transferred to a hospital or to the care of a new doctor at home. This is a major cause of digitalis poisoning. The fallacies of clinical judgment and of the patient's memory are better avoided by means of a telephone than an electrocardiograph. If there is any uncertainty, large single doses are almost never justified. If the preparation, dosage and

times of previous administration can be established, a rough estimate of additional requirements can usually be made. Further doses should be on the conservative side of this estimate.

The exact dose of any digitalis preparation necessary for the *optimal* therapeutic effect in any patient can be determined only by a clinical assay of the drug in that particular patient. However, the dose that will produce a definitely beneficial effect in most patients and yet produce only minor toxicity in a few has been reasonably well established. A single oral dose of 1.2 mg. of digitoxin to each of 512 cardiac patients produced gastrointestinal symptoms in only 15 (2.8 per cent). A comparable single dose of digitalis leaf produced nausea or vomiting in 20 per cent, and a single dose of 2.0 mg. of digitoxin to 98 patients produced similar symptoms in 32 per cent. Dangerous manifestations of toxicity did not develop in any of these patients.[74] These and other studies indicate that, for digitoxin at least, an effective level of digitalization can be induced within less than 12 hours with a wide margin of safety. Nevertheless, this is rarely a necessary or a wise procedure. Although previous digitalis medication may be denied, sometimes mistakes are made. If vomiting does occur, an unknown amount of the drug may be lost, and even gastrointestinal symptoms are undesirable at best. If the series is large enough, sooner or later rapid "complete digitalization" will result in disaster. It has also been shown[74] that a daily dose of 0.2 mg. of digitoxin will effectively digitalize within a period of two or three weeks. For the patient who has developed mild congestive failure over a long period of time, and who can be reexamined weekly, this is an entirely satisfactory treatment procedure. Usually, however, it is desirable to achieve a definitely beneficial effect within 24 to 48 hours, with a maximum of safety. For the patient under close observation, 0.4 mg. of digitoxin may be given every six to eight hours for three doses, noting the effects of each dose before the next is given. Thereafter, smaller doses are given at the same or longer intervals until an optimum effect is achieved, or evidences of early toxicity appear. Digitalis dosages, in grams, may be substituted for digitoxin dosages, in milligrams, for either of these therapy technics.

The principal guide to the optimum level of digitalization is rarely clearly defined. It consists of a clinical judgment of the relief of the manifestations of the congestive failure. In the presence of atrial fibrillation, the apical pulse rate is a useful index, with limitations noted above. Manifestations of toxicity (except local gastrointestinal effects which appear within two hours after drug administration) usually indicate that the point of maximum benefit has been reached or passed. In some patients, particularly those who are severely ill, the toxic and therapeutic ranges may overlap, and maximum benefits are achieved in the presence of minor toxicity. In most patients, digitalis is helpful at doses well below the toxic range. Considered over a period of time, the slight benefits of higher dosage do not justify the discomforts and hazards that may develop. It is sometimes wise, however, to approach the toxic level at least once, as a trial, because the therapeutic dividend may be surprising.

Prolonged maintenance of optimum levels of digitalization, like initial digitalization, is an experiment in each individual. A reasonable estimate of dosage requirements is made; then, as subsequent developments dictate, it is revised. An occasional patient will be helped by, and will tolerate no more than, 0.05 mg. of digitoxin daily. Equally rarely, as much as 0.3 mg. is required and tolerated. In the majority of patients, 0.15 mg. daily is a satisfactory dose, and is usually recommended as a starting level. The guides to optimum maintenance are the same as those for initial digitalization. Several weeks may be needed for an error in dosage in either direction to be apparent. About one patient in three will require subsequent revision, more often downward than upward. The dosage for satisfactory maintenance, once established, does not ordinarily fluctuate widely unless there is a change in the physical state of the patient.

Digitalis, U.S.P., and digitoxin, U.S.P. are by far the most widely used of the several

preparations available for initial and maintenance therapy. They are the most slowly effective of the group. This is rarely a disadvantage, for in the vast majority of instances, a few hours is not a significant delay. Their effects are also the most persistent. This is a distinct advantage insofar as it results in stability of the level of digitalization, once achieved. It is a disadvantage in that toxicity once it develops, lasts longer. Digitalis produces more local gastrointestinal irritation than digitoxin, and is probably not quite so uniform in potency from lot to lot. It may be more likely to produce noncardiac systemic manifestations of toxicity before cardiotoxicity appears. If so, this has been considered an advantage by some, who believe that the cardiotoxicity appears more frequently without warning when digitoxin is used. Conversely, the maximum therapeutic benefits may be denied by troublesome nausea and vomiting with digitalis. Nevertheless, either of these preparations is highly satisfactory for most digitalization needs.

Some physicians prefer other preparations derived from digitalis for initial digitalization and prolonged maintenance. The basis for this preference must rest upon a very few proven differences between the drugs. Eight criteria of acceptability of a digitalis preparation are listed by Goodman and Gilman.[54] Two of these, ease of administration and drug stability, are equally well met by all preparations. A third, adequate intestinal absorption, is probably met by all. Since the absorption of the other preparations, with the exception of lanatoside C, fall within the range between digitalis (20 per cent) and digitoxin (100 per cent), it is not reasonable to claim superiority over both. A fourth factor is cost. A year's supply of any of these preparations costs the average patient less than 10 dollars. A fifth factor is uniformity of potency. The purified glycosides are probably more uniform than the whole leaf preparation, but the differences are of borderline clinical significance. A sixth criterion is effective myocardial action. No convincing evidence has been presented in animals or in man that any one of these preparations differs appreciably from any other in this regard. A seventh criterion pertains to the margin of safety between effective therapeutic dose and toxicity. A mass of convincing data conclusively shows that all digitalis preparations have approximately the same margin of safety.[54, 55]

Recently, an exception to this generalization has been reported by Batterman, DeGraff and Rose.[75, 76] From their studies they reached the conclusion that the difference between therapeutic and toxic doses is greater with gitalin (amorphous) than with any other digitalis preparation. Hejtmancik and Herrmann[77] did not confirm this observation, but they were impressed by the value of gitalin in the management of several patients who responded poorly to other preparations. It is of interest that when toxicity did occur, nausea, vomiting, or other extracardiac manifestations preceded evidences of cardiotoxicity in only 12 of 29 cases; the reverse was observed in nine, and in eight they appeared concurrently. Asymptomatic cardiotoxicity from gitalin has also been noted elsewhere.[78] Other recent reports have been favorable,[79, 80] but investigators in the past have been unimpressed.[81] In animal preparations, comparing therapeutic and irritability doses with lethal doses, gitalin was not found to be unique.[82] If further studies convincingly demonstrate a superiority of gitalin (amorphous) with respect to toxicity, it should eventually displace other preparations currently in use. The evidence does not justify such a conclusion at this time. Controlled investigation of comparative toxicity and therapeutic effects, in which neither the patient nor the evaluating physician know the drug or its dosage, should be helpful in the clarification of this important point.

The eighth and final criterion is the rates of accumulation and elimination which permit digitalization at varying speeds and the maintenance of optimum cardiac effects over long periods. Special merits, if any, must be based chiefly upon this criterion. Each of the other preparations listed affect the heart more rapidly than does digitalis or digitoxin. Since the effects of each succeeding dose develop more quickly, they may be more clearly defined and more quickly used to judge the next dose. Also, the danger line may be approached with greater safety, because if toxicity

TABLE 1.—*Approximate Doses of Various Cardioactive Preparations for Oral and Intravenous Use (See Text)*

Preparation	Initial Digitalization				Maintenance	
	Oral		I. V.		Oral	
	Average	Range	Average	Range	Average	Range
	Grams	Grams			Grams	Grams
Digitalis U.S.P.	1.2	1.0–2.0			0.15	0.05–0.30
	mgm.	mgm.	mgm.	mgm.	mgm.	mgm.
Digitoxin U.S.P.	1.2	1.0–2.0	1.2	1.0–2.0	0.15	0.05–0.30
Acetyl Digitoxin N.N.R.	2.0	1.5–2.5	1.5	1.3–2.0	0.3	0.1–0.6
Gitalin (amorphous) N.N.R.	5.0	4.0–8.0	—	—	0.5	0.25–1.0
Digoxin U.S.P.	2.0	1.0–4.0	1.0	0.8–1.6	0.5–0.75	0.25–1.0
Lanatoside C U.S.P.	6.0	5.0–10.0	1.6	1.2–1.6	1.0	0.5 –2.0
Ouabain U.S.P.	—	—	0.8	0.5–1.0	—	—
Acetyl Strophanthidin	—	—	0.6*	?	—	—

* *Maximum* dose for a single injection, to be diluted and administered in not less than five minutes. The average total dose for full digitalization is approximately 1.2 mg.

develops, it soon abates, which is a factor of considerable importance if toxicity is severe. These arguments have some merit as they pertain to the management of a patient who is very ill and must be carried on the borderline of serious toxicity in order to obtain maximum benefits of the drug; nevertheless, the advantages over the slower acting preparations are small, at best. Few patients get or need the constancy of attention required to take advantage of these supposed superiorities. Rapid action and short persistence may occasionally be used to advantage in a severely ill patient in whom it is suspected that the maintenance dosage of digitalis or digitoxin is inadequate. One or two small doses of digoxin, added to the regular maintenance schedule, may provide the basis for a rapid answer with a minimum of hazard. These properties are also of some advantage in the management of paroxysmal atrial tachycardia, fibrillation or flutter in which maintenance is a small problem once a satisfactory initial effect has been achieved.

Oral dosages of several preparations for initial digitalization and for maintenance are shown in table 1. The average figures, given in divided doses and spaced over 24 to 48 hours, will produce definite therapeutic effects in most patients, with a wide margin of safety in all, with the important exceptions noted above. The dosages indicated are somewhat lower than those found in many tables, which list the average optimum dose. The general plan for initial digitalization with any of these preparations is the same as that described for digitoxin and digitalis: slow administration if the patient is to be re-examined at long intervals, administration of the average figure in divided doses over 24 to 48 hours for a patient under careful observation, or in less than 24 hours if the demand is urgent. If further dosage is then needed for optimum effect, the amount listed under average maintenance dose may be given every six to eight hours, carefully observing the effects of each dose.

In a patient who is unable to take or retain oral medication, digitalis preparations may be used intravenously with but little added risk, provided that small doses are injected slowly, with an adequate interval for observation between doses. If digitoxin is used, the doses are the same by the intravenous as by the oral route. With all other preparations, the intravenous dose is appreciably smaller than the oral dose, as shown in table 1. For maximum safety, effective digitalization should not be attempted in less than 48 hours, with an additional period for establishing optimum levels.

Burrell and Coggins[83] describe the lethal consequences of an intravenous injection of acetyl strophanthidin. Ventricular fibrillation developed suddenly, with none of the usual prefibrillatory warnings. Catastrophies of this sort are rare, but they have been reported from

the rapid, especially from the intravenous, administration of many drugs, even when the total dose is not excessive. With digitalis preparations, it is always possible to err in predicting the size of a dose. Rapid intravenous digitalization should be avoided unless the demands for speed are extremely clear. Unless the situation is so critically urgent that a few hours cannot be allowed to pass for oral drug effects, the dangers of intravenous digitalization should not be accepted.

When demands are extreme, as in severe pulmonary edema associated with rapid atrial fibrillation or flutter or paroxysmal atrial tachycardia, intravenous digitalization may be lifesaving. In such an emergency, intravenous lanatoside C, or digoxin are effective within a few minutes. When it is certain that a digitalis preparation has not already been used, one half the average *intravenous* digitalizing dose may be given in one dose, injected in a five-minute period, followed *if necessary*, by half as much in each of two hourly doses. Thereafter, further administration must be deferred for six hours for the full effects to develop. Some prefer ouabain, which is even more rapid. An initial dose of 0.5 mg. is followed each half hour by 0.1 mg. for two doses, then hourly by 0.1 mg. for a maximum of three doses. These are the *absolute maximum* rates and amounts of administration. When these or any other of the intravenous preparations are used, the patient must be most carefully observed. When the emergency phase has passed, further digitalization, if necessary, should proceed at a slower rate, and orally. After ouabain, especially, transition to a more stable preparation, without toxicity or loss of therapeutic effects, may be difficult.

Occasionally, the most astute clinician is unable to be sure whether a desperately ill patient would be benefitted by more digitalis, or conversely, whether toxicity is already present. In such a dilemma, the choice lies between stopping further drug administration and waiting until toxic effects, if present, may have abated, or administering a small dose of a rapidly acting preparation (digoxin, lanatoside C, or ouabain) in the hope that if improvement does not result, the aggravation of the toxicity will be rapidly apparent, and also rapid in its disappearance. Either course may be hazardous. Lown and Levine have suggested that potassium first be administered. Improvement would then confirm the suspicion of toxicity; but if there is no improvement, acetyl strophanthidin may be used as a trial drug. The procedures to be followed and the interpretation of the results are described.[16] Acetyl strophanthidin should be used with full recognition of its potentially lethal hazards.[16, 83, 84] Administered intravenously, it is extremely rapid in action with peak effects in less than 20 minutes, and complete disappearance of effect in four hours at most.[85]

VII. The Manifestations of Digitalis Toxicity

Severe toxicity is certainly more common than it was only a few years ago, although, in the opinion of this writer, it is neither so ubiquitous, so persistent, nor so regularly disastrous as some recent reports might indicate. The principal reason for increased incidence of toxicity is plain. More patients are now receiving digitalis preparations in larger doses, more rapidly administered. The standard maintenance dose of 0.1 Gm. of leaf has declined in popularity, and the days of 15 drops daily of tincture (equivalent to about six minims or 0.04 Gm. of leaf) are gone. Daily doses equivalent in potency to 0.15 or 0.2 Gm. of leaf are now widely used. Whereas the benefits of the digitalis preparations have been more widely realized, the ill effects are understandably more frequent. Minor manifestations of toxicity are, to a degree, useful, marking the sometimes overlapping boundaries of therapeutic effectiveness and the danger zone. Major toxicity is usually the result of obviously excessive dosage or careless inattention to warnings.

Unusual individual variations in tolerance to digitalis preparations account for occasional, but important toxicity. The causes of these variations are often obscure. In some instances they are predictable or at least understandable. Advanced hepatic or renal disease may sufficiently reduce degradation and excretion to reduce digitalis requirements slightly. The thyrotoxic patient will usually require a

reduction in digitalis dosage as thyrotoxicity is controlled. Similarly, after I^{131} therapy in an euthyroid patient, digitalis requirements may be considerably diminished. The digitalis tolerance and needs of the patient in severe cardiac failure are generally considered to be above average, but some of these patients are unusually sensitive, especially if body potassium has been depleted, spontaneously or with the help of various therapeutic measures. The hazard of calcium administration to a digitalized patient has also been discussed above. Finally, it may be that differences do exist between the essential toxic potentialities of different digitalis preparations, and that minor toxicity warnings are more evident with one than with another. If so, these would account for only an occasional example of the major toxicity that is seen in clinical practice.

The manifestations of toxicity may be obvious, or they may be so similar to those of the underlying disease that differentiation between the two is both difficult and important. The appearance of any toxic symptom or sign (excluding local gastrointestinal irritation effects) is a forewarning that serious toxicity, either cardiac or extracardiac, may ensue with any increase in dose.

Extracardiac Manifestations of Toxicity. These serve as useful warnings, provided they do not of themselves seriously impair the well being of the patient at drug levels below those required for full cardiotherapeutic benefits.

(1) The gastrointestinal manifestations of toxicity are the most frequent: anorexia, nausea, vomiting, or occasionally diarrhea. Abdominal fulness and discomfort from toxicity are easily confused with those caused by the visceral engorgement of cardiac failure itself. When any of these symptoms appear within one or two hours after an oral dose, they are usually caused by local gastrointestinal irritation and need not be confused with true toxicity. Otherwise they are usually of central origin, and, therefore, of greater significance. Digitalis causes both local and systemic symptoms more frequently and at smaller doses than most of the other preparations.

(2) Visual disturbances, "snow" or yellow vision, are not often mentioned voluntarily by the patient, but are elicited in response to questioning. Yellow vision occurs most frequently, but not exclusively, with whole leaf digitalis preparations.

(3) Neurologic symptoms are occasionally observed,[86] especially headache or neuralgias of the face and upper extremities. Withdrawal of digitalis may result in a surprising relief of these symptoms.

(4) A variety of vague symptoms may take the place of more specific toxicity manifestations. General weakness and lassitude, insomnia, and irritability, for example, are especially likely to occur in the aged or debilitated. The vagueness of this "wilting" may obscure both its specific cause and its considerable therapeutic importance.

(5) True idiosyncrasy to digitalis preparations is very rare; thrombocytopenic purpura has been described.[87] The statement by a patient that he cannot tolerate any digitalis preparation, even in the smallest doses, must be accepted with reservation.

Cardiotoxicity from Digitalis Preparations. Serious effects of digitalis on the heart may become manifest in a progression of cardiac failure. This may not be attended by other, more specific indications of toxicity; but when other manifestations have reached major proportions, especially those associated with arrhythmias, the benefits of therapy are customarily lost. The end-all of cardiotoxicity is ventricular fibrillation, but digitalis may produce almost any form of disturbance of rhythm.

(1) Sinus bradycardia may occur, but it is a poor guide to the adequacy of therapy. Sinus arrest or sinoatrial block may or may not be preceded by bradycardia.

(2) Atrial premature beats are less frequent than ventricular premature beats. Occasionally an established ectopic atrial rhythm develops at a rate only slightly faster than the previous sinus rhythm; it is easily mistaken for sinus tachycardia. With increased toxicity, the rate increases. At atrial rates of about 150 to 170, atrioventricular block appears, sometimes with Wenkebach phenomena, sometimes with a regular 2:1 ratio, sometimes quite erratically. This form of toxicity, paroxysmal atrial tachycardia with or without block, is mistaken both clinically and electrocardiographically for

rapid fibrillation or "impure flutter." Such a mistaken diagnosis may lead to further digitalization, with lethal consequences. It is an important clinical syndrome, noted in earlier reports[88, 89] and described in detail by Lown and Levine.[16]

(3) Atrioventricular conduction disturbances usually begin as a prolongation of the P-R interval and progress to complete A-V block. Ventricular slowing in atrial fibrillation is usually a valuable therapeutic index. With toxicity, the ventricular rate may become excessively slow, or it may rise as the result of the activity of ectopic pacemakers, either ventricular or nodal.

(4) Ventricular premature beats precede classical bigeminy or trigeminy, multifocal ventricular ectopic beats, ventricular paroxysmal tachycardia, flutter, and finally fibrillation. One or several steps in this sequence may be skipped.

(5) A variety of other conduction disturbances and ectopic rhythms may occur, but it is noteworthy that bundle branch block is rarely a manifestation of digitalis toxicity.

Electrocardiographic changes, other than those specifically associated with the arrhythmias described above, characteristically occur with digitalis therapy. They may be transient after exertion, and thereby result in a false positive exercise tolerance test for angina.[90] The magnitude of these electrocardiographic changes *in any one individual* may provide a guide to the relative level of digitalization in that individual, and has provided a criterion for biologic assay of digitalis preparations in humans.[91] However, major cardiotoxic effects may occur in the absence of well developed "digitalis patterns," or the patterns may be very pronounced in an individual who has no associated evidence of toxicity.

VIII. The Management of Digitalis Toxicity

Slight anorexia or nausea, the pulse a little slow or an occasional premature beat have long been used as warnings and guides in digitalis therapy. Beyond this level, hazardous toxicity may be feared, and further benefits are not to be expected. These events indicate the need for a day or two of drug withdrawal, followed by resumption of maintenance at a slightly lower dosage level. When manifestations are somewhat more severe, withdrawal should be for a longer time and new maintenance levels should be set appreciably lower. Minor toxic signs and symptoms will usually abate or disappear within two to three days at most.

Hazardous toxicity is usually associated with rapid digitalization in excessive dosages, a major change in the physical status, or neglect of the warnings of minor toxicity. Severe vomiting or other extracardiac manifestations of toxicity may seriously complicate severe heart failure. Obviously, digitalis must at once be discontinued. Giving potassium may be of some specific benefit; it certainly reduces the danger of superadded cardiotoxicity if potassium is at all depleted, as it is likely to be in the presence of vomiting, diarrhea, or restricted dietary intake. Otherwise management of major extracardiac toxicity is entirely symptomatic. Major cardiotoxicity infrequently develops without warning, but once it is established an already deficient cardiac output may be so seriously reduced that the consequences are lethal, or ventricular fibrillation may occur. Since therapeutic measures are of themselves somewhat hazardous, the vigor of their application requires fine clinical judgment of the severity of toxicity and whether the level of digitalization is still on the upgrade or is declining. The duration of toxicity is related to the biologic persistency of the preparation employed, but even with severe toxicity from the most stable preparations, digitoxin or digitalis leaf, marked improvement or complete relief is the rule within three or four days at most. Exceptionally, toxicity may persist for a week or more. If improvement is slower, a cause other than digitalis toxicity should be suspected as the basis for the persistence of the symptoms.

Effective emergency treatment measures are available for the dangerous arrhythmias of digitalis poisoning. Constant professional attention is demanded, with the electrocardiograph continuously connected for records at frequent intervals. Oxygen should be given, and tourniquets, sedation and l-norepinephrine should be available for use as needed. Unless

there is reason to believe that hyperkalemia is present, potassium should be given either orally as chloride or citrate (4 Gm. in cold fruit juice, followed if necessary by 2 Gm. hourly for two hours) or, and this is preferable, given intravenously. The standard intravenous preparation contains potassium chloride, 3 Gm. (13 mEq. per Gm.) in 20 cc. of water. This solution should be diluted to 500 cc. in 5 per cent glucose solution. It may be given at a maximum rate of 5 cc. per minute until a total of 6.0 Gm. has been injected. The perfusion should stop if the arrhythmia is controlled. These rates of administration and total dosages may be increased in patients with frank potassium depletion, but otherwise should not be exceeded in the first six hours. Further potassium administration may be required to prevent return of the arrhythmia until the digitalis has been destroyed or excreted.

In ventricular paroxysmal tachycardia caused by digitalis poisoning, procaine amide is indicated if potassium is not immediately available, or if no effect has been achieved in three hours. Three standard capsules (750 mg.) of procaine amide may be given orally, followed if necessary by 250 mg. hourly for two additional doses. If the patient is unable to take or retain oral medication, 50 mg. every two minutes may be given in a continuous drip until 300 mg. have been given, then the rate is reduced to 50 mg. every four minutes to a maximum total of 1000 mg. in one hour. Procaine amide is available in 10 cc. vials containing 1000 mg. of the drug. Blood pressure should be taken every minute during intravenous administration. The infusion must be slowed if the pressure falls appreciably, or stopped entirely if the fall is alarming, as occasionally happens. If the pressure does not promptly return towards the preinjection figures, l-norepinephrine should be given.

Conclusion

Some of the most important aspects of the use of digitalis may be thus summarized. Any standard digitalis preparation, if used with reasonable care and skill, will produce excellent results in the majority of treatment problems. Proper use of the drug is more important than proper selection of the preparation, since, except for variation in accumulation and decline of effects, the drugs differ little. A growing tendency toward excessive use of rapidly acting intravenous preparations should be discouraged; it is unnecessary and dangerous. The value of these preparations, skillfully used when clearly indicated, has been offset by the harmful effects of indiscriminate use in inexperienced hands. Rapid improvement is better than slower improvement only when it is also safer.

Most instances of dangerous toxicity can be traced to mismanagement, though, even under the direction of the most competent physician, toxicity can occur. The importance of electrolyte disturbances in promoting digitalis poisoning deserves emphasis. Recognition of certain supraventricular tachycardias as manifestations of toxicity will prevent the hazardous consequences of further digitalis administration. From personal experience, toxicity from digitalis leaf or digitoxin is not so persistent nor so troublesome as some have stated, and stability of maintenance has been easier than with the more biologically labile preparations. Lanatoside C, digoxin, and gitalin (amorphous) have some advantages in the management of the severely ill patient who can be kept under close observation, and in the treatment of some of the arrhythmias. Acetyl digitoxin appears to be a compromise between the two groups.

No substitute for the digitalis drugs is on the horizon. They are of incalculable value in the every day life of millions of human beings. Perhaps, with more care and wisdom in the use of these drugs, many patients may be helped a little more and a few a great deal more.

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ABSTRACTS

BACTERIAL ENDOCARDITIS

Quinn, R. W. and Brown, J. W.: Bacterial Endocarditis. Arch. Int. Med. **94:** 679 (Oct.), 1954.

A case is presented of a patient with bacteremia due to *Streptococcus viridans* and *Brucella abortus*. It is probable that the patient had brucellosis with bacterial endocarditis due to *Streptococcus veridans*, although endocarditis due to both organisms cannot be ruled out. The patient recovered after therapy which included chlortetracycline (Aureomycin), streptomycin, and sulfadiazine and has remained well.

BERNSTEIN

Waisbren, B. A.: Antibiotic Treatment of Bacterial Endocarditis Due to Enterococcus. Arch. Int. Med. **94:** 846 (Nov.), 1954.

A case of bacterial endocarditis due to an Enterococcus was treated successfully with a combination of erythromycin, chlortetracycline, and streptomycin. This combination was found in vivo and in vitro to exhibit bacteriostatic potentiation and a bactericidal additive effect against the causative strain of Enterococcus. This combination of antibiotics was more bacteriostatic than penicillin and streptomycin in five other strains of enterococci. It was also more bactericidal than penicillin and streptomycin against three of these five strains. These results suggest that when a case of bacterial endocarditis due to enterococcus does not respond to penicillin and streptomycin the combination of erythromycin and chlortetracycline or of erythromycin, chlortetracycline, and streptomycin might be of benefit.

BERNSTEIN

BLOOD COAGULATION

Sercar, P.: Plasma Volume, Bleeding and Clotting Time on Hypothermic Dogs. Proc. Soc. Exper. Biol. & Med. **87:** 194 (Oct.), 1954.

The effect of hypothermia on the plasma and cell volume of blood, bleeding time, and clotting time was studied on 44 mongrel dogs. In well controlled experiments it was found that hypothermia to 23 to 25 C. caused a statistically significant prolongation in bleeding and clotting times.

HARVEY

Bassiouni, M.: The Estimation of Heparin and Similar Substances in Human Blood and Tissues Using a Combined Biological and Colorimetric Method with Paper Electrophoretic Studies. J. Clin. Path. **7:** 330 (Nov.), 1954.

A method is presented for the extraction of heparin from human tissues. Results of tissue analysis show differences in the content of heparin in adult tissue and tissue from the new born.

HARVEY

Moses, C., and Rhodes, G. L.: The Effect of Heparin on Cholesterol Partition, Lipoproteins and Atherosclerosis in Experimental Hypercholesterolemia. Angiology **5:** 429 (Oct.), 1954.

In rabbits with experimentally induced hypercholesterolemia of marked degree, the development of aortic atherosclerosis was not altered by the administration of depoheparin in 10 mg. doses intramuscularly three times weekly for eight weeks.

WESSLER

CONGENITAL ANOMALIES

Maxwell, G. G. and Crumpton, C. W.: The Taussig-Bing Syndrome. A Report of Two Further Cases,

One Complicated by Aortic Coarctation. Am. J. Med. **17:** 578 (Oct.), 1954.

Taussig and Bing in 1949 described a new congenital heart syndrome in which the aorta arises entirely from the right ventricle, with the pulmonary artery originating from the left chamber while straddling a ventricular septal defect. The authors present two new cases. One had almost complete coarctation of the aorta between the left common carotid and the left subclavian artery, with patent ductus. Associated with this was deep cyanosis of the right upper extremity and absent pulse on the left. Angiocardiography is probably the best method of definitive diagnosis in the Taussig-Bing syndrome since the levoposition of the pulmonary artery is readily demonstrable.

HARRIS

Silver, M. L.: Hereditary Vascular Tumors of the Nervous System. J.A.M.A. **156:** 1053 (Nov. 13), 1954.

The hereditary tendency in angiomatous disease of the nervous system has been noted by all observers who have studied the condition now known as hemangiomatosis (Lindau's disease). Pathological specimens of patients with vascular tumors of the nervous system indicates these are capillary-cavernous hemangiomas often associated with cysts. In time they may accumulate lipid material and resemble hypernephroma. Treatment depends on the location of the tumor and its growth potential. The occurrence of these tumors is known in a single family through seven generations. Their presence must be suspected in members of any family with the diagnosis of hemangiomatosis (Lindau's disease). The disease is transmitted as a Mendelian dominant, is not sex linked, and is one of the few inherited neoplasms of man.

KITCHELL

CONGESTIVE HEART FAILURE

Whol, M. G., Brody, M., Shuman, C. R., Turner, R., and Brody, J.: Thiamine and Cocarboxylase Concentration in Heart, Liver, and Kidney, of Patients with Heart Failure. J. Clin. Invest. **33:** 1580, (Nov.), 1954.

Thiamine deficiency has been demonstrated in congestive heart failure by various direct and indirect means. Wohl and associates determined the content of thiamine and cocarboxylase (the active form of thiamine) in various tissues of patients with and without cardiac failure. The heart, liver and kidney tissues were examined in 12 cases of long-standing failure who received the usual treatment but no supplementary vitamins. The results were compared with 10 non-cardiac patients who died from brain tumor, coronary occlusion, cerebral hemorrhage. In all three tissues a lower concentration of total thiamine and cocarboxylase was found in patients with heart failure as compared with those who died of other causes. Statistical differences were significant only in the heart (for both substances) and in liver (for thiamine alone).

This indication of thiamine deficiency suggests that inadequate intake, poor absorption or enhanced excretion (as by diuretics) of the vitamin may be involved. The possible influence of the reduced thiamine-cocarboxylase content of heart muscle on myocardial metabolism deserves further study.

WAIFE

CORONARY ARTERY DISEASE

Johns, T. N. P. and Olson, C. J.: Experimental Myocardial Infarction: I. A Method of Coronary Occlusion in Small Animals. Ann. Surg. **140:** 675 (Nov.), 1954.

The authors described a method for studying the coronary arterial network in small animals and presented the results of ligating one or both main coronary arteries. Using such a procedure, myocardial infarction with survival resulted in a high percentage of cases in the mouse, hamster, rat and guinea pig.

It was concluded that despite various disadvantages imposed by the smallness of rodents, the described method of coronary occlusion produces a test infarct which is more nearly standard than any currently available.

ABRAMSON

Schnur, S.: The Current Dispute Concerning Anticoagulants in Acute Myocardial Infarction. J.A.M.A. **156:** 1127 (Nov. 20), 1954.

Although the committee for the evaluation of anticoagulants of the American Heart Association recommended in its initial report in 1948 that "anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless a definite contraindication exists," the American Heart Association itself has never officially recommended routine anticoagulant therapy. It appears there is more disagreement now regarding the correct management of these patients than when the report originally was published. This article poses 21 questions which are commonly asked about anticoagulants and gives detailed answers. It is pointed out that the process of intravascular thrombosis is extremely complex and involves both unknown and known factors. To this problem is added the problem of which patient to treat. The solution of the last problem would lead to more rational therapy in which possibly 10 per cent of patients would be treated with 100 per cent effectiveness instead of routine treatment in all patients which may be effective only in 10 per cent of the cases.

KITCHELL

Flack, H. A., Mart, J. A. and Maher, C. C.: Electrocardiographic Patterns in Patients With Second Myocardial Infarctions. Quart. Bull. Northwestern Univ. M. School **28:** 252 (Fall), 1954.

Clinical and electrocardiographic records of 12 patients who sustained a posterior infarction followed by an anterior infarction were studied. A new anterior infarct superimposed upon an old posterior infarct showed the conventional serial pattern changes without undue delay. The serial electrocardiographic defects of the newer infarct materially changed the residual pattern of the old infarct.

Accurate diagnosis of the second infarction (anterior), and the previous posterior, depends upon the availability of serial electrocardiograms. The residual defects were those of both, of only the older posterior, or of only the old anterior, or there were no defects of either infarction.

BERNSTEIN

Wilson, J. L. and Knudson, K. P.: Infarction of the Cardiac Atria. New England J. Med. **251:** 599–561 (Sept. 30), 1954.

A man, aged 31 years who suffered an acute myocardial infarction and died on the seventh day of illness is described in detail. The postmortem examination disclosed evidence of infarction in the anterior and lateral aspects of the left ventricle and the anterior wall of the left atrium including the appendage. A mural thrombus was attached to the endocardium on the anterolateral wall of the appendage. The localization of the areas of infarction was suspected ante mortem on the basis of electrocardiographic changes.

The changes in the electrocardiogram which are said to be suggestive of atrial infarction include an elevation or depression of the PR segment, depending upon the localization of the zone of atrial infarction, and the sudden development of atrial dysrhythmias. The complications of atrial infarction include the various atrial dysrhythmias, mural thrombi with resultant embolic phenomena and aneurysmal dilatation of the atrial wall, with subsequent rupture.

ROSENBAUM

Russek, H. I., and Zohman, B. L.: Chances for Survival in Acute Myocardial Infarction. J.A.M.A. **156:** 765 (Oct. 23), 1954.

The authors divided cases of acute myocardial infarction into "good risk" and "poor risk" cases according to whether or not they had had (1) previous myocardial infarction, (2) intractable pain, (3) extreme degree or persistence of shock, (4) significant enlargement of the heart, (5) gallop rhythm, (6) congestive heart failure, (7) auricular fibrillation or flutter, ventricular tachycardia or intraventricular block, and (8) diabetic acidosis, marked obesity, previous pulmonary embolism, varicosities in the lower extremity, thrombophlebitis (past or present) or other states predisposing to thrombosis. Of the total group of 1,318 cases, it was found that 611 (46.4 per cent) could be classified as "good risk" patients. The death rate in this group was found to be only 3.4 per cent. Of the 21 fatalities in this group, 10 occurred suddenly within the first 48 hours after admission so that mortality rate during the subsequent periods of hospitalization when 11 fatalities occurred was only 1.8 per cent. Thrombotic or thromboembolic complications occurred in only 1.3 per cent of the "good risk" patients. Of the total group, 53.6 per cent presented poor prognostic signs and were classified as "poor risk" patients. The death rate in this group was 60 per cent and the incidence of thrombotic and thromboembolic complication was 11.5 per cent. Anticoagulant therapy would appear to confer no benefit in "good risk" patients because of the low incidence of thromboembolism. In the more serious cases, however, anticoagulants do appear to exert a favorable influence on both mortality and morbidity statistics. The initial 48 hours following an attack represents a critical period and there is risk in too early or unnecessary removal of the patient to the hospital. Clinical appearance of the patient at the onset of the attack is the best index to the future course of his illness. Overconfidence and carelessness are not warranted as a result of these findings.

KITCHELL

Russek, H. I., and Zohmann, B. L.: "Selective" Versus "Routine" Use of Anticoagulants in Acute Myocardial Infarction. J.A.M.A. **156:** 1130 (Nov. 20), 1954.

It appears that anticoagulant therapy is neither necessary or desirable for patients who sustain their first acute attack of myocardial infarction and present no unfavorable criteria for recovery at the time of first examination. However, the appearance of poor prognostic signs in these patients should be regarded as a clear indication for the use of anticoagulants. Only about 30 per cent of all patients require anticoagulant therapy but this low figure should not detract from the established value of such treatment in "poor risk" cases. The age of the patient should not be considered an important factor indicating or contraindicating the use of anticoagulants in acute myocardial infarction. There is already sufficient evidence to justify "prognostic classification" at the beginning of an attack as a means of selecting patients for anticoagulant therapy in acute myocardial infarction.

KITCHELL

Beck, C. S., and Leighninger, D. S.: Operations for Coronary Artery Disease. J.A.M.A. **156:** 1226 (Nov. 27), 1954.

The history of coronary artery disease may be divided into 3 periods. First is the period of clinical recognition which dates back about 40 years. Second is the period of revascularization which began in the experimental laboratory in 1932 and which has received slow but steady recognition. Third is the period of prevention which is for the future. Only a small beginning has been made in the experimental laboratory in prevention. The causes of death in coronary disease are of two types: mechanism death and muscle death. Surgical operations cannot stop the occlusive process or restore degenerated myocardium. Operation can prevent death by increasing the supply of blood by only 2–3 cubic centimeters in trigger areas which may set off a mechanism disturbance.

Two operations to increase blood flow are established on the basis of the experimental work. The number 1 operation consists of abrasion of the epicardium and lining of parietal pericardium, application of an inflammatory agent (0.2 Gm. of powdered asbestos) to these surfaces, partial occlusion of the coronary sinus where it enters the right auricle, and grafting of parietal pericardium and mediastinal fat to the surface of the heart. The number 2 operation consists of first shunting arterial blood into the coronary sinus by a free vein graft between the aorta and the coronary sinus or by direct anastomosis between these structures. Two or three weeks later the second stage of this operation is done and consists of partial occlusion of the coronary sinus where it enters the right auricle. This partial occlusion raises the blood pressure in the sinus and produces retrograde flow. Experiments with the ligation-mortality-infarct method have established the fact that these operations reduce both the mortality and the size of the infarct after occlusions providing the operation is done before the artery is ligated. In evaluating these operations for humans, the authors believe the most acceptable type of patient is the lean person in his forties or fifties who has had the disease for a year or more, having pain but still able to get around. Operation is not done within six months of an infarct. Patients with heart failure and patients in whom the heart is giving way and enlarging are not candidates for operation. Patients with status anginosis and with moderate enlargement of the heart are acceptable. It appears now that 4 our of 5 patients return to work after operation with little or no pain and the risk of operation has been reduced. At the time of this writing, of 27 patients operated on in 1954, one died from thoracotomy alone and one died after a coronary operation on the second day. These patients had severe degenerative disease of the heart.

KITCHELL

Johnson, A. S., Firnschild, P. G. and Fulton, H.: Visualization of Coronary Sinus Graft and Venous Pathways of the Heart In Living Dogs. Am. J. Roentgenol. **72:** 648 (Oct.), 1954.

Thirty operations were performed in dogs and a Beck II aortico-coronary sinus fistula was produced. In nine of these retrograde aortography was performed by introducing contrast medium into the left common carotid artery, and eight exposures were made at half second intervals. The results in two of these aortographies were technically unsatisfactory. Two other dogs died, one from cerebral edema, the other from gross hemorrhages at the site of the graft (four days postoperatively). In the remainder the coronary sinus graft and venous pathways were adequately visualized.

One third of the animals were digitalized, and the second stage of the operation (where the coronary sinus is narrowed) was omitted. None of these animals developed congestive heart failure. In another third of the series, where no digitalis was administered congestive heart failure was frequent. In the third group both stages of the operation were performed at the same time, the results were good. The authors recommend elimination of the second stage of the operation.

SCHWEDEL

Oka, M.: Some Observations on the Cholinesterase Activity of Plasma in Myocardial Infarction. Acta med. scandinav. **150:** 313–320 (Nov. 30), 1954.

Changes in the plasma cholinesterase activity were observed in seven patients suffering from acute myocardial infarction. The studies were made over periods ranging from 10 to 36 days. The cholinesterase estimations were made according to Michel's original electrometric method. In all of the cases studied there was a fall in the cholinesterase activity of the plasma after myocardial infarction with an increase occurring during the patient's recovery. There was a clear correlation between the plasma cholinesterase activity and the erythrocyte sedimentation rate with decreased values of the former corresponding to increased values of the latter and vice versa. There was no clear correlation between the plasma cholinesterase activity and the leucocyte changes nor was the plasma cholinesterase activity altered by the administration of morphine or atropine. In the febrile cases there was a greater fall in the plasma cholinesterase activity and a more marked increase in the erythrocyte sedimentation rate than in the non-febrile cases. The author expressed the opinion that this test is of value in diagnosis and also in prognosis in myocardial infarction since a continual decrease in plasma cholinesterase activity is an unfavorable sign whereas rising values indicate that recovery is proceeding.

ROSENBAUM

Gordon, S.: Dupuytren's Contracture: The Significance of Various Factors in its Etiology. Ann. Surg. **140:** 683 (Nov.), 1954.

The author studied a series of 369 patients having Dupuytren's contracture in an attempt to determine possible etiologic factors. He noted that the greatest number of cases was in patients between the ages of 55 and 75. Tuberculosis was believed to have some significance in the development of the lesion. However, neither sex, occupation, arthritis, diabetes, epilepsy nor myocardial disease could be implicated as possible causes for the disorder.

ABRAMSON

Waldron, B. R., Fennell, R. H., Jr., Castleman, B. and Bland, E. F.: Myocardial Rupture and Hemopericardium Associated with Anticoagulant Therapy. New England J. Med. **251:** 892–894 (Nov. 25), 1954.

This report is based upon the study of 545 autopsied cases of recent myocardial infarction, 79 of which were associated with hemopericardium. Slightly less than half of them were observed prior to the first use of anticoagulants in 1946. Of the 302 cases treated after 1946, 71 received anticoagulants and 241 were not so treated. The incidence of hemopericardium with or without myocardial rupture was not significantly different in the two periods in the patients who did not receive anticoagulants. However, in those who did receive anticoagulants, there was a threefold rise in the prevalence of hemopericardium without rupture and a twofold increase in the occurrence of myocardial rupture. There was no difference in the time elapsed between the onset of symptoms of myocardial infarction and rupture in the treated and the untreated groups.

Mural thrombi occurred with equal frequency in the treated and untreated groups, a feature that made improbable the hypothesis that altered coagulation failed to accomplish sealing of a small defect or tear which might be the initial lesion of a myocardial rupture. In a single case, death resulted from massive hemopericardium with tamponade without myocardial rupture in a patient whose prothrombin concentration was reduced to a point below 10 per cent with Dicumarol. In another patient treated with Dicumarol, but with prothrombin levels in the therapeutic range, death resulted from tamponade due to hemorrhage from a coronary artery which ruptured at the site of the thrombus. It is emphasized that the risks, as well as the advantages of anticoagulant therapy of acute myocardial infarction, must be borne in mind.

ROSENBAUM

ELECTROCARDIOGRAPHY

Carlotti, J., Loannides, P. Birnbaum, S. and Sicot, J. R.: Electrocardiographic Disorders in the Course of Cardiac Catheterization. Arch. mal. coeur **47:** 833 (Oct.), 1954.

The authors reviewed their material of simultaneous pressure and electrocardiographic recordings in 633 cases submitted to cardiac catheterization with respect to incidence and dynamic effects of cardiac arrhythmias occurring in the course of the procedure, and their potential dangers. There were no fatalities. In practically all cases ventricular premature systoles were induced by the catheter. There were several instances of more severe types of arrhythmias, viz., runs of ventricular tachycardia or auricular fibrillation or flutter invariably with rapid termination without embarrassing the patient. The same was true for occasional onset of right bundle branch block or of A-V dissociation. In some cases the disturbances of rhythm started before the catheter entered the cavities of the heart which is ascribed by the authors to a "particular irritability of the heart" in certain patients. The conclusions arrived at from this study are that cardiac catheterization potentially can create dangerous situations because of the induction of a severe arrhythmia, but on the whole can be considered a benign procedure in cardiac diagnosis.

PICK

Chiche, P. and Abiteboul, J.: The Electrocardiogram in Calcareous Alterations of the Aortic Valves. Arch. mal. coeur **47:** 816 (Oct.), 1954.

The authors report electrocardiographic findings in 70 cases with calcareous alterations of the aortic valve, 21 proven at autopsy, the rest radiologically. Eleven cases showed an entirely normal tracing or a borderline pattern. Definite abnormalities found in the others consisted almost invariably in signs of left ventricular hypertrophy, associated or complicated by alterations suggesting diffuse subendocardial ischemia or complicated by intraventricular and A-V conduction defects. The two latter complications are variable but permit the differentiation from certain other conditions causing a left heart strain pattern. Thus, according to the authors, a T inversion in the left precordial leads is hardly found in pure rheumatic aortic insufficiency, and develops in hypertension only when the latter is complicated by coronary disease, or when hypertension takes a rapid progressive "malignant" course. On the other hand, in syphilitic aortic regurgitation the electrocardiogram frequently resembles that seen in calcific aortic stenosis.

The electrocardiographic pattern of calcific aortic stenosis appears to be determined by two factors, a permanent one caused by the obstacle to left ventricular outflow and a labile functional factor depending on the degree of impairment of coronary circulation developing and varying in the course of the disease.

PICK

Pastor, B. H.: Elimination of Electrocardiographic Distortion Due to Somatic Tremor. J.A.M.A. **156:** 314 (Sept. 25), 1954.

One of the common artefacts that make electrocardiographic interpretation difficult is due to termor of the somatic muscles. A simple technic for elimination of the distorting effect of tremor involves the use of a set of self-retaining electrodes such as the one described by Welsh. The electrodes are applied to the shoulders and thighs of the patient instead of on the extremities. This is technically satisfactory since an electrode placed anywhere on an extremity records as though it were at the junction of the extremity with the trunk.

KITCHELL

Giraud, G. Latour, H. and Puech, P.: Electrocardiography of the Sinus Coronarius—Part I: General Study and Casual Pathology. Arch. mal. coeur **47:** 900 (Nov.), 1954.

Electrocardiograms recorded following introduction of a venous catheter tipped by an electrode, into the coronary sinus, are described and illustrated. The procedure was performed, by chance or by purpose, without accident in 37 subjects with various types of abnormalities in the conventional electrocardiographic leads.

The obtained records resemble, in general, electrograms obtained in animals and in man directly from the surface or the cavities of the heart. The method has the advantage of recording left ventricular potentials without the danger associated with retrograde catheterization of the left heart. The close contact of the electrode, introduced into cardiac veins with the surface of the various chambers, permits determination of the time characteristic of the intrinsic deflections in various locations. The actual duration of auricular and ventricular complexes can be exactly measured and corrections made for measurements in ordinary leads. Further advantages consist of establishing more precise criteria for hypertrophy of single chambers, in particular of the right ventricle, differentiation of hypertrophy from conduction defects of other etiology, and recognition of combinations of the two, or hypertrophy in more than a single chamber.

PICK

ENDOCRINE EFFECTS ON CIRCULATION

Ledingham, J. M.: The Influence of the Adrenal on the Water and Electrolyte Disturbances Following Nephrectomy, and its Relation to Renoprival Hypertension. Clin. Sc. **13:** 535 (Nov.), 1954.

The distribution of water, sodium and potassium in the intra- and extracellular compartments of heart and skeletal muscle was studied in two groups of nephrectomized rats, in one of which adrenalectomy had also been performed. The animals were kept on a mixed diet, with either tap water or 0.5 per cent saline. Body extracellular fluid volume increased in all groups approximately equally. In the groups drinking water, there was evidence for an extrarenal action of the adrenals in controlling osmolarity of the expanded fluid volume. This was probably accomplished by withdrawal of sodium from skeletal muscle and partly by depressing the desire for water. The effects on blood pressure were variable within all groups, except that the nephrectomized group drinking 0.5 per cent saline became significantly hypertensive. It appeared that the adrenals, acting in the absence of the kidneys, withdrew sodium from the cells to maintain the level of extracellular sodium, and in these circumstances, renoprival hypertension occurred.

ENSELBERG

Herrman, R. G., Flamboe, G. E., and Cohen, K. K.: The Effect of Nine Cardiac Steroids and Epinephrine on the Respiration of Heart Muscle Slices. J. Pharmacol. & Exper. Therap., **12:** 23 (Sept.), 1954.

Glycosides in certain concentrations are known to increase the respiration of heart muscle slices of some species. The effect of nine cardiac steroids plus epinephrine in various molar concentrations ranging from 1×10^{-8} to 1×10^{-4} was studied on the heart muscle respiration of a single species (cat). All steroids caused a sustained increase in cardiac respiration, but the onset and peak of the increase depended on the glycoside concentration, the higher concentrations causing both to occur at an earlier time. The potency of these drugs varies in the following order from most active to least active; ouabain, cymarin, desacetylanghinin, acetyltanghinin, strophanthidin, strophanthidin-3-benzoate, strephanthidinic acid, thevetin and uzarin. Epinephrine and ascorbic acid failed to cause any change in the respiration of cat heart muscle.

These results suggest a fair correlation between in vivo cardio-toxic action and in vitro respiratory response of these compounds. In addition, small changes in their chemical structure caused great changes in their activity.

WECHSLER

Luetscher, J. A. Jr. and Johnson, B. B.: Observations on the Sodium-Retaining Corticoid (Aldosterone) in the Urine of Children and Adults in Relation to Sodium Balance and Edema. J. Clin. Invest. **33:** 1441 (Nov.), 1954.

Using bioassay methods it is possible to measure sodium-retaining activity of material extracted from the urine. There is evidence that this material closely resembles the corticoid, aldosterone. Significant activity was observed in urinary extracts from edematous patients with lipemic nephrosis, hepatic cirrhosis and cardiac failure. The level of sodium-retaining activity seemed to be related to the sodium output, rather than to a specific disease, urine flow or state of hydration.

The stimulus to the hormone production does not appear to be pituitary corticotrophin but rather "inadequacy" of the circulation including depletion of plasma or extracellular volume.

WAIFE

Rosenman, R. H., Freed, S. C. and Smith, M. K. Effect of Cortisone upon Vascular Responsiveness of Potassium-Deficient and Normal Rats. Proc. Soc. Exper. Biol. & Med. **87:** 292 (Nov.), 1954.

Hypotension was induced in intact rats by dietary deprivation of potassium. Cortisone administration to such rats rapidly restored their blood pressures to normotensive levels. This study suggests that the restorative effect of cortisone upon blood pressure of potassium-depleted, hypotensive rats is not accounted for by augmentation of vascular responsiveness to pressor substances.

BERNSTEIN

de Langen, C. D.: Basal Metabolism and Sodium Chloride. Acta med. scandinav. **150:** 257–261 (Nov. 30) 1954.

Changes in the basal metabolic rate in patients with Addison's disease were studied. It was found that the basal metabolism was abnormally low in these patients prior to treatment. When sodium chloride alone was given the metabolism became normal. When the diet contained a sufficient quantity of sodium chloride the addition of Doca or cortisone had no appreciable effect upon metabolism. When the metabolism had been restored to normal with a combination of sodium chloride and hormones and the hormones were withdrawn, the metabolism continued to be normal in two cases and became lower in a severe case, being restored to normal later when hormones were added once more. In view of these observations, the effect of sodium chloride deficiency upon basal metabolism was studied in three normal subjects. Each subject was placed on a strict saltless diet for 10 days and then subjected to daily Turkish baths for 6 to 10 days. This is said to have lowered the basal metabolism in all three subjects with immediate recover after sodium chloride consumption. The author concludes that this effect is mediated through influence upon capillary activity and tissue flow. The question is raised that a surplus in the daily consumption of sodium chloride may cause a pathological disturbance of the capillaries although no experimental evidence is brought out bearing on this particular point in this communication.

ROSENBAUM

HYPERTENSION

Stunkard, A. J., Eurman, G. H., Wachspress, M. and Wertheim, A. R.: Treatment of Hypertensive Disease with Hydralazine. Comparison of its Action with that of Low Sodium Diet in Hospitalized Patients. Am. J. Med. **17:** 712 (Nov.), 1954.

Reporting a controlled study of the effects of hydralazine in the hospital treatment of twenty-five patients with essential hypertension, the authors achieved a significant reduction in blood pressure in seventeen patients (68 per cent) over an average of thirteen weeks. There was regression of such changes as hypertensive retinopathy and cardiac failure in less than 25 per cent of these patients. Side reactions in most, and tolerance in some patients, require careful regulation of dosage and supportive measures. Hydralazine probably should not be used in patients with evidence of coronary or cerebral artery disease. Comparison with treatment by low sodium diet reveals hydralazine to be of somewhat lesser therapeutic potency. This advantage may be compensated by the greater ease of management of the drug.

HARRIS

Hatch, F. T., Wertheim, A. R., Eurman, G. H., Watkin, D. M., Froeb, H. F. and Epstein, H. A.: Effects of Diet in Essential Hypertension. III. Alterations in Sodium Chloride, Protein and Fat Intake. Am. J. Med. **17:** 499 (Oct.), 1954.

A four-year investigation of the Kempner rice regimen in the treatment of hypertension conducted in a hospital environment under controlled conditions indicates that the effective anti-hypertensive principle is the restriction of sodium ion. In patients with essential hypertension in whom beneficial effects of stringent NaCl deprivation have been obtained, clinical improvement may be preserved on a more liberal diet than the Kempner rice regimen. Addition of 3 Gm. of NaCl daily to the rice diet from the time of its institution prevented any lowering of blood pressure. In patients with a significant anti-hypertensive response to the rice or special low-sodium diets the addition of 0.5 Gm. NaCl daily did not usually elevate the blood pressure. Addition of larger amounts of NaCl usually did evoke significant rises in blood pressure. In patients with a favorable response to the unmodified regimen no loss of beneficial effects was noted when 12 to 50 Gm. per day of low-sodium protein, 20 to 40 Gm. per day of fat and 200 Gm. per day of vegetables were added singly or together to the diet. Decreases in blood pressure similar to those obtained with the rice diet occurred in three patients who were given a special low-sodium diet without previous treatment with the Kempner regimen.

HARRIS

Kahn, E. A.: Twenty Years' Experience with the Surgery of Hypertension. New England J. Med. **251:** 633–638 (Oct. 14), 1954.

The author reviews his experience with supradiaphragmatic splanchnic section for essential

hypertension and makes particular reference to a series of 268 cases in which the dissection was carried from the twelfth dorsal to, or above, the sixth dorsal segment as a one-stage procedure. This was done by Dr. M. M. Peet in a period from 1946 to 1949. The operative mortality in this group was 3 per cent. Of these patients, 241 were followed for five to eight years. During this period, 57 died, 101 had good results and 33 had an excellent result as indicated by a normal blood pressure. It is mentioned that when patients with severe headache are subjected to splanchnic section, the complaint almost invariably disappears even when the blood pressure is not reduced. The author feels that if the blood pressure is extremely high or is tending to climb, especially in men, and if it does not respond to medical treatment, operation should be advised, even in patients between the ages of 50 and 55 years, if symptoms are severe. It is felt that it is still not proved that it is necessary to carry the dissection below the diaphragm to remove lumbar ganglions to produce a maximum lowering of the blood pressure. It is mentioned that "total sympathectomy" may be advantageous in patients with angina pectoris, tachycardia and vasospastic states of the upper extremities. Splanchnic section should be performed with caution in patients with peptic ulcer or severe gall-bladder disease. Chylothorax occurred as a complication in 8 cases of approximately 2500 subjected to supradiaphragmatic splanchnic section.

ROSENBAUM

Schroeder, H. A.: Management of Arterial Hypertension. Am. J. Med. **17:** 540 (Oct.), 1954.

Enough potent antihypertensive substances are now available to lower the elevated blood pressure in all cases of arterial hypertension effectively. The main questions are "How should it be controlled?," "To what extent?" and "What are the hazards of control?" In controlling the severe stages of hypertension the neurogenic sympathetic influence must be blocked or abolished and the pressor substances in the blood simultaneously inactivated. Acting on the central nervous system are Rauwolfia serpentina and its alkaloid, reserpine. Hexamethonium and pentapyrrolidinium block the ganglionic transmission of sympathetic and parasympathetic impulses, presumably by competing with some natural quaternary ammonium compounds. The desirable effect is upon the sympathetic ganglia, the undesirable upon the parasympathetic. Protoveratrine acts upon the parasympathetic nervous system in some manner not thoroughly understood, possibly upon the higher centers, the carotid sinus or vagus. The net result is stimulation. The drug also acts upon the vomiting center in doses close to therapeutic ones. Hydralazine, acting on vascular smooth muscle or kidney, apparently controls the nephrogenic factor. Pherentasin is directly inactivated by this agent and the pressor action of some but not all primary amines inhibited in a manner not understood. This drug affects the neurogenic factor little if at all, except in very large doses. Renal vasodilatation in the face of a lowered blood pressure occurs. The known actions of the hydrazines include binding of certain heavy trace metals, combination with sulfhydryl compounds, and attachment to carbonyl groups. Amino acid decarboxylase is inhibited in vitro.

Using hexamethonium and hydralazine in combination (Hyphex), Schroeder presents the results of their use in 304 severe hypertensive patients. Severe benign and malignant hypertension regressed into mild or moderate stages in all cases adequately treated. Reserpine was also useful. Combination therapy of two or more drugs were usually required. Limits of effectiveness of the method lay in the production of renal insufficiency.

HARRIS

Alexander, N., Henshaw, L. B. and Druvy, D. R.: Development of a Strain of Spontaneously Hypertensive Rabbits. Proc. Soc. Exper. Biol. & Med. **86:** 855 (Aug.–Sept.), 1954.

A colony of rabbits was raised using as original breeding stock naturally occurring hypertensive rabbits of hybrid strains. Careful measurements of blood pressures were made on these rabbits over several years time. It was found that there was a high incidence of elevated systolic blood pressure in the offspring of these rabbits. This systolic rise is characterized by only moderate elevation, naturally occurring fluctuation, and increasing height with advancing age.

HARVEY

Diaz, C. J., deLa Barreda, P., Molina, A., and Alcala, R.: Use of New Technic to Study Humoral Transmission of Hypertensive Effects of Vagal Stimulation. Proc. Soc. Exper. Biol. & Med. **86:** 745 (Aug.–Sept.), 1954.

Cross circulation was effected in dogs by connecting the central end of the aorta of the one dog with the peripheral end of the other dog and vice versa. Simultaneous carotid and femoral pressures were recorded. Injection of a circulatory hypertensive hormone (nor-adrenalin) into the femoral vein of one dog caused increase in the carotid pressure of the treated dog followed by increase in the femoral pressure of the untreated dog. The femoral pressure of the treated dog was unaffected. Quite different, however, was the response to stimulation of the central end of the cut vagus in the one dog. In this situation the pressure in the stimulated dog of both the carotid and femoral arteries rises followed by a less marked rise in the pressure of the femoral artery of the unstimulated dog. The authors believe this is evidence that there is a hypertensive

substance liberated from the arterial walls themselves.

HARVEY

Birkhead, N. C., and Allen, E. V.: Comparison of Effects on Hypertension of Hexamethonium and Pentapyrrolidinium Injected Subcutaneously. Proc. Staff Meet., Mayo Clinic. **29:** 489 (Sept.), 1954.

The ability of the bitartrate salt of Pentapyrrolidinium to lower blood pressure of a group of hypertensive patients was studied and the duration of its effect was compared with the duration of effect of a comparable dose of hexamethonium. Pentapyrrolidinium bitartrate did not consistently produce a more prolonged effect than hexamethonium; in several instances duration of effect was less.

Although side effects are not specifically included in the data, they did occur with both drugs in a few instances, and consisted mainly of lightheadedness which was experienced by several patients on standing. The response of the hypertensive patients to the ganglionic blocking agents varied widely.

SIMON

Gifford, R. W., Jr., Allen, E. V. and Birkhead, N. C.: Pentapyrrolidinium Bitartrate (M. & B. 2050A) in the Treatment of Hypertension: Preliminary Observations. Proc. Staff Meet., Mayo Clinic. **29:** 496 (Sept.) 1954.

Pentapyrrolidinium bitartrate which is a ganglionic blocking agent with potent hypotensive properties has been employed in treatment of 24 patients. By giving this drug either by mouth or by subcutaneous injection the authors have been successful in reducing significantly the blood pressure of 23 of 24 patients with severe hypertension so treated. Thirteen hypertensive patients have been under treatment with pentapyrrolidinium for periods of 1 to 7 months and satisfactory control of the blood pressure has been maintained in all. This has been accompanied by symptomatic improvement, restoration of cardiac compensation when previously impaired and regression in the hypertensive changes in the retinas of most of the patients.

The incidence and severity of side reactions to pentapyrrolidinium which include constipation, orthostatic weakness and dryness of the mouth, have been disappointingly great. From this study they have concluded that the use of pentapyrrolidinium should be restricted to patients with severe hypertension that has failed to respond to simpler treatment and should be initiated only for hospitalized patients by physicians familiar with the capriciousness of ganglionic blocking agents.

SIMON

Stevenson, D. and Sjoerdsma, A.: Blood Pressure in Patients with Hypertension following Intramuscular Chlorpromazine. Proc. Soc. Exper. Biol. and Med. **86:** 726 (Aug.–Sept.), 1954.

The effect upon the blood pressure of chlorpromazine was investigated in ten adults with benign essential hypertension. The drug was administered intramuscularly. There was no effect of the blood pressure taken in the recumbent position, but there was lowering of the systolic pressure in all, upon standing, which persisted for four hours. There was also a lowering of the diastolic pressure in six of these individuals.

HARVEY

Fremont, R. E.: Hypertensive Crisis and Severe Myocardial Ischemia Induced by Piperoxan, with Comments on the Differential Diagnosis and Treatment of Hypertensive Crises. Angiology **5:** 381 (Oct.), 1954.

A patient with hypertension and established coronary artery disease with old myocardial infarction developed electrocardiographic evidence of myocardial ischemia after receiving piperoxan intravenously. The hazards of this drug in patients with coronary artery disease is discussed.

WESSLER

Ledingham, J. M.: Hypertension and Disturbances of Tissue Water, Sodium and Potassium Distribution Associated with Steroid Administration in Adrenalectomized Rats. Clin. Sc. **13:** 543 (Nov.), 1954.

Studies were made on groups of adrenalectomized rats, drinking either water or 1.5 per cent saline, and treated with DOCA, cortisone, or a combination of both. The blood pressure response to cortisone differed from that to DOCA in that it was more uniform, occurred more quickly, and remained at a maximum level. In groups of rats drinking 1.5 per cent saline, simultaneous treatment with DOCA and cortisone resulted in greater hypertension than expected from either steroid alone. This effect was also observed in animals drinking water, and in animals with intact adrenals.

Electrolyte disturbances occurred as expected. For example, adrenalectomized rats drinking water showed a fall in extracellular fluid volume and plasma sodium, and there was no evidence of entry of sodium into heart or skeletal muscle. Other electrolyte studies pointed up the lability of intracellular sodium and potassium in skeletal muscle as compared with cardiac muscle. It appears that expansion of the extracellular fluid volume is not an essential for the development of hypertension. Nor is there evidence that intracellular hydration is concerned with hypertension. Though there is no consistent pattern of fluid electrolyte disturbance in steroid hypertension, it is noted that there is one disturbance common to three types of experimental hypertension (renal, adrenal steroid, and renoprival)—that is a relatively higher extracellular

than intracellular sodium concentration in the heart muscle. Whether this has causal relationship to hypertension is not known.

ENSELBERG

PATHOLOGIC PHYSIOLOGY

Roberts, K. E., Randall, H. T., Farr, H. W. and Kidwell, A. P.: Cardiovascular and Blood Volume Alterations Resulting from Intrajejunal Administration of Hypertonic Solutions to Gastrectomized Patients: The Relationship of These Changes to the Dumping Syndrome. Ann. Surg. **140:** 631 (Nov.), 1954.

A study was made to clarify the mechanisms responsible for the dumping or postgastrectomy syndrome (the sensation of fullness and churning in the epigastrium followed by or associated with weakness, sweating, tachycardia, tachypnea, pallor and an elevated blood pressure). Hypertonic solutions or a test meal were given to 10 patients who had undergone total gastrectomy, four who had had subtotal gastrectomies and one who had a feeding jejunostomy. Six patients with intact stomachs were used as controls.

Intrajejunal administration of hypertonic solutions caused an acute decrease in circulating blood volume resulting from a shift of plasma water into the intestinal lumen. Electrocardiographic alterations and symptomatology typical of the dumping syndrome were noted coincidental with the decrease in blood volume. Similar changes did not occur in patients with intact stomachs who were given equivalent amounts of hypertonic solution.

It was suggested that the acute drop in blood volume, with subsequent stimulation of pressoreceptors associated with regulation of arterial blood pressure, was implicated in the sympathetic component of the dumping syndrome.

ABRAMSON

Kao, F. and Ray, L. H.: Regulation of Cardiac Output in Anesthetized Dogs During Induced Muscular Work. Am. J. Physiol. **179:** 255 (Nov.), 1954.

In these experiments "neural dogs" may be defined as follows: exercising legs which are connected to the body only by nerves. Another dog, connected to the exercising legs only by vessels is designated a "humoral dog." Cardiac output of neural dogs increases more than that of intact controls during exercise. A-V oxygen differences and ventilation-perfusion ratios are decreased. In the humoral dogs the output is also increased. Here however, the A-V oxygen differences are increased. This last is interpreted to mean that humoral factors alone are insufficient to regulate output during exercise. A failure of the peripheral circulation results.

OPPENHEIMER

McConn, R. G., Beazley, H. L., Hughes, W. M. and Moyer, J. H.: Renal Hemodynamic Response to Acute Alterations of Blood Pressure with Vasopressor and Vasodepressor Agents. Texas J. Med. **50:** 712 (Oct.), 1954.

It was demonstrated that when normotensive dogs were rendered hypertensive by the intravenous administration of norepinephrine, a significant reduction in glomerular filtration rate and renal plasma flow occurred. Comparable studies were done in nine normotensive humans using norepinephrine. A reduction in renal plasma flow occurred when these patients were rendered hypertensive, but glomerular filtration rate was not similarly reduced. Norepinephrine is effective in improving renal function in normovolemic shock and in some cases of hemorrhagic shock.

Determination of glomerular filtration rate as related to mean blood pressure reduction was accomplished in 17 patients with untreated hypertension. In both the hypertensive and the normotensive patients, there was a decrease in glomerular filtration rate as the blood pressure was reduced. In patients with hypertension, when the blood pressure is lowered into a normal range (mean blood pressure of 95 mm. of mercury), the glomerular filtration rate is depressed far below the control value. In comparison, when the blood pressure of the normotensive group is reduced to a hypotensive range (mean blood pressure of 71 mm. of mercury), the glomerular filtration rate remains well within the range of normal and shows only a 14 per cent reduction from the control value.

BERNSTEIN

Kay, J. H.: Experimental Production of Pulmonary Stenosis. Arch. Surg. **69:** 651 (Nov.), 1954.

The chronic physiologic and pathologic changes following experimental pulmonary stenosis were studied in a series of 29 dogs. The valvular changes were produced by the application of fuming nitric acid to the pulmonary cusps. Of the series, four died in right heart failure. Three of these showed a pronounced rise in right ventricular pressure but no change in pulmonary artery pressure. In all the animals, autopsy revealed right ventricular hypertrophy and inelasticity of the proximal portion of the pulmonary artery, with narrowing of the vessel immediately distal to the insertion of the cusps.

ABRAMSON

Wilson, R. H., Hoseth, W. and Dempsey, M. E.: Respiratory Acidosis. 1. Effects of Decreasing Respiratory Minute Volume in Patients With Severe Chronic Pulmonary Emphysema, With Specific Reference to Oxygen, Morphine and Barbiturates. Am. J. Med. **17:** 464 (Oct.), 1954.

In patients with prolonged elevation of P_aCO_2 the respiratory center loses its normal degree of

sensitivity to carbon dioxide. Hypoxia then becomes the dominant stimulus to respiration. Breathing 99.6 per cent oxygen removes this hypoxic stimulation to respiration and decreases significantly the respiratory minute volume and effective alveolar ventilation. Subsequently the P_aCO_2 becomes elevated and the pH of the blood is depressed to a lower level. Uncompensated respiratory acidosis supervenes. In the more diseased states coma ensues.

Morphine and barbiturates in small doses may depress the minute volume and effective alveolar ventilation in patients with pulmonary emphysema. Morphine adversely affects patients with emphysema in three ways: (1) The respiratory center in the presence of morphine responds less rapidly to higher levels of P_aCO_2 and a lower pH. (2) The carotid body fails to stimulate respiration normally in the presence of further hypoxemia. (3) The central nervous system is depressed to the extent that the Hering-Breurer reflex fails adequately to assist respiration in the normal way. Respiratory acidosis with coma readily develops in these patients because they retain large quantities of carbon dioxide in the pulmonary alveoli and arterial blood.

HARRIS

Kouvenhoven, W. B. and Milnor, W. P.: Treatment of Ventricular Fibrillation Using a Capacitor Discharge. J. Appl. Physiol. **7:** 253 (Nov.), 1954.

The purpose of this investigation was to develop a simple effective capacitor discharge apparatus for the treatment of ventricular fibrillation without performing a thoracotomy.

Capacitor discharges were passed directly through the heart of open chested dogs by means of electrodes placed on the right and left ventricle and by means of electrodes fastened to opposite sides of the chest in closed chest dogs. Ventricular fibrillation was produced and then defibrillation was attempted by these capacitor discharges.

In closed chest dogs, capacitor discharges of greater energy (500 watt-seconds) were required for successful defibrillation than in the open chested dogs (5 watt-seconds). These results were obtained when the fibrillation persisted for less than 40 seconds. Low energy capacitor discharges were more likely to produce ventricular fibrillation than high energy discharges.

WECHSLER

Denson, J. S. and Joseph, S. I.: Cardiac Rhythm and Endotracheal Intubation—a Clarification. Anesthesiology **15:** 650 (Nov.), 1954.

The authors obtained continuous electrocardiographic tracings during 110 intubations of the trachea in patients under cyclopropane anesthesia. In 106 instances, no change in cardiac rhythm was observed either during laryngoscopy or with the passage of the tube through the vocal cords into the trachea. The four instances of arrhythmias observed at this time in two patients were related to apnea rather than to passage of the airway into the trachea. In 87 patients, there was no change in the rhythm during the period immediately following intubation, and in 19, ventricular arrhythmias appeared six seconds to four minutes after intubation. In all of the cases, the original rhythm was restored only by increasing or improving pulmonary ventilation (adequate supply of oxygen and elimination of carbon dioxide). On the basis of these observations, it is postulated that the significant factors responsible for the arrhythmias observed with endotracheal intubation are either carbon dioxide excess, oxygen deficiency, or both, and not reflex mechanisms as has been commonly believed.

SAGALL

Smith, J. A., Glassman, M., Lind, A. H., Post, M., Sohn, H. and Warren, S.: Effects of Ouabain on Beat and Oxygen Consumption of Embryonic Chick Hearts. Proc. Soc. Exper. Biol. & Med. **86:** 747 (Aug.–Sept.), 1954.

Embryonic chicken hearts, dissected free and placed in a Ringer bath, were observed and by a suitable arrangement oxygen consumption measured. Ouabain, added to the bath in low concentrations, caused a rise in oxygen consumption proportional to the concentration. In higher concentrations it not only increased oxygen consumption, but caused an increase in the rate of the beat and finally irregularities in its rhythm. Atropine, added to the bath, decreased the severity of these irregularities without altering oxygen consumption.

HARVEY

von Ahn, B.: The Acute Effect of Tobacco Smoking and Nicotine on the Electrocardiogram Especially During Induced Hypoxia. Acta med. scandinav. Supplement **292:** 1–112, 1954.

The author reviews the literature pertaining to the effect of tobacco upon the heart and the electrocardiogram. From the reports recorded, smoking in most cases produces an increase in heart rate with a simultaneous flattening of the T waves not exceeding 1 to 2 mm. in the standard limb leads. It is believed that these changes are the result of increased sympathetic tone rather than to coronary insufficiency. The author reports his observations on a group of 59 subjects ranging from 20 to 28 years in age and a second group of 27 patients ranging from 38 to 57 years in age. Studies were made during hypoxia, cigarette and cigar tests both with and without hypoxia, following the intravenous injection of nicotine during hypoxia and with exercise on a bicycle ergometer during hypoxia. Control observations were carried out in all instances. In a 17 to 18 minute hypoxia test breathing a mixture of 6.5 per cent oxygen, 4.5 per cent carbon dioxide and 89 per cent nitrogen, a spon-

taneous flattening of the T waves was recording which was designated the time-factor, and which occurred in spite of constant heart rate and constant oxygen saturation. Smoking during hypoxia resulted in a slight or moderate increase in heart rate with a simultaneous flattening of the T waves and a slight depression of the S-T segment. The intravenous injection of 1 to 3 mg. of nicotine produced essentially the same changes as smoking but also resulted in increased hyperventilation and, in the larger doses, euphoria or other evidence of intoxication. Arrhythmias consisting of extrasystoles were observed rarely during smoking with hypoxia. The effect of smoking or nicotine during hypoxia is considered in part "physiologic" through stimulation of the sympathetic ganglia and in part "pathologic" in that it may cause through some nervous and humoral mechanism a reduction in coronary flow to the point at which coronary insufficiency develops during the hypoxia test.

The author is of the opinion that the electrocardiographic changes associated with smoking are due to increased sympathetic tone. This belief is supported by the observation that the "pathological" electrocardiographic changes of heavy smoking or nicotine can be simulated by the injection of adrenaline. Furthermore, in certain cases the development of electrocardiographic changes usually provoked by smoking can be almost completely prevented by the use of dihydroergotamine. Exercise produced flattening of the T waves similar to that after nicotine in one-half of the cases studied and in the other half there was more marked decrease in the height of the T waves after exercise. It was concluded that the electrocardiographic changes induced by smoking or the injection of nicotine during hypoxia were due chiefly to the simultaneous increase in the heart rate. In the occasional cases in which heavy smoking or the injection of nicotine resulted in flattening of the T waves without associated increase in heart rate, the response was attributed to increased adrenal secretion. However, in the rare cases of acute nicotine poisoning which have been recorded in which the changes observed have included serious arrhythmias, various forms of heart block and, rarely, changes in the R-T segment together with abnormally high, sharp T waves, it is believed that the alterations are due to some electrolyte imbalance, possibly hypopotassemia. The author is doubtful that the electrocardiographic changes observed in persons with clinically healthy hearts following smoking or the injection of nicotine are of coronary origin.

A distinction is made between "tobacco angina" and "angina pectoris precipitated by tobacco-smoking." The former is said to be common in heavy smokers, both normal persons and those with cardiac disease; it does not develop in immediate association with smoking, it lasts for one to several hours, is of long duration and is not of coronary origin. The latter is a rare syndrome occurring only in patients with coronary artery disease, always develops in immediate relation to tobacco-smoking, is characterized by pains clearly of coronary origin and associated with pathological electrocardiographic changes.

ROSENBAUM

Cutler, J. G., Nadas, A. S., Goodale, W. T., Hickler, R. B. and Rudolph, A. M.: Pulmonary Arterial Hypertension with Markedly Increased Pulmonary Resistance. The Pulmonary Vascular Obstruction Syndrome. Am. J. Med. **17:** 485 (Oct.), 1954.

Pulmonary arterial hypertension results from either an increase in pulmonary blood flow with relatively normal resistance or, conversely, of an augmented pulmonary vascular resistance with relatively normal or even diminished pulmonary blood flow. This paper presents a group of seven patients with maximal increase in pulmonary vascular resistance who comprise a clinically homogeneous group. They gave a history of exertional dyspnea; early cyanosis was noted in all but one. The only constant cardiac finding on physical examination was the marked accentuation of the second pulmonic sound. X-rays and electrocardiograms revealed right ventricular hypertrophy. The pulmonary vasculature was prominent at the hilum and normal or diminished at the periphery of the lung fields. All cases showed pulmonary arterial hypertension with increase in pulmonary vascular resistance to at least systemic levels. Arterial unsaturation was present in all. The clinical picture resembles that of essential pulmonary hypertension except that the authors do not exclude patients with congenital heart disease. The common denominator in all their patients was the maximally increased pulmonary vascular resistance, i.e., pulmonary vascular obstruction. In the differential diagnosis of this syndrome, congenital heart disease patients with large left to right shunts, with or without pulmonary arterial hypertension, are most important to consider. This group can be distinguished from the pulmonary vascular obstruction syndrome by the x-ray finding of significant cardiac enlargement and the uniformly plethoric lung fields. This group must also be distinguished from patients with "secondary" increase in pulmonary arteriolar resistance or valvular pulmonic stenosis and patent foramen ovale or a ventricular septal defect. The authors suggest that patients with maximally increased pulmonary vascular resistance should be classified as a separate group, irrespective of whether or not they have congenital heart disease. No known treatment exerts significant influence on the course or prognosis of pulmonary vascular obstruction.

HARRIS

AMERICAN HEART ASSOCIATION, INC.

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AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS

Arrangements are nearing completion for the AHA's 31st Annual Meeting and 28th Scientific Sessions to be held in New Orleans, October 22–28. Indications are that the program will be the most extensive and varied ever arranged by the Association.

The Scientific Sessions and the programs of the Council on Community Service and Education and the Council on Rheumatic Fever and Congenital Heart Disease will largely be conducted at the New Orleans Municipal Auditorium, October 22–24. Subsequent events, including the Assembly panels, the annual meeting of the Assembly and the Staff Conference of Heart Associations are to be held at the Jung Hotel. Other events scheduled for the Hotel include the AHA Annual Dinner, Sunday evening, October 23, the luncheon session of the Council on Community Service and Education, Sunday, October 23, the annual Assembly luncheon, Tuesday, October 25, and the Staff Conference luncheon, Thursday, October 27.

Scientific Sessions

Two outstanding features of the Scientific Sessions will be the Lewis A. Conner Memorial Lecture, Saturday, October 22, and the George Brown Memorial Lecture, Sunday, October 23. The Conner Lecture will be presented by George A. Perera, M.D., Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, whose subject will be Primary Hypertension. The Brown Lecture will be delivered by George Burch, M.D., Henderson Professor of Medicine, Tulane University School of Medicine. His subject will be Digital Rheo-Plethysmography.

Community Service Programs

The Second Annual Meeting of the Council on Community Service and Education will include programs dealing with the relationship of body weight and heart disease, chaired by Herbert Pollack, M.D., New York, and on rehabilitation, chaired by E. A. Irvin, M.D., Dearborn, Mich. These programs will be presented on Sunday, October 23, as will the luncheon session of the Council during which Martin Cherkasky, M.D., will review the accomplishments and objectives of the group.

On Monday, October 24, the Community Service Council will join with the Council on Rheumatic Fever and Congenital Heart Disease to present a program featuring discussions of rheumatic fever prevention and of the problems of cardiac and suspected cardiac children in the schools. Participation in this program is being arranged by Bernard Walsh, M.D., Washington, D. C.

Assembly and Staff Conference

Assembly panel discussions, in which many of the key problems confronting Heart Associations will be discussed, are scheduled for Tuesday, October 25. The panels will take up direct and patient care services, fund raising, Heart Association relationships, personnel and research. The Annual Meeting of the Assembly, top governing body of the Association, will be held on Wednesday, October 26. This meeting will elect AHA officers and board members, and will be marked by the installation of Irvine H. Page, M.D., Cleveland, as President to succeed E. Cowles Andrus, M.D., Baltimore.

The Staff Conference of Heart Associations will begin on Wednesday afternoon and continue through Thursday morning. The conference will bring together staff members from the National Office and from affiliated Heart Associations and their chapters. In addition, workshops on public information and fund raising will be held on Thursday afternoon and Friday morning for those who wish to attend.

Exhibits

Because of the decision to hold the Scientific Sessions in the Municipal Auditorium, a greatly increased number of exhibits will be possible. Current plans call for 48 displays.

Registration and Program

Reservation forms for the Annual Meeting and Scientific Sessions are available from the AHA or from local Heart Associations. These forms, which provide for hotel reservations, should be returned directly to the Jung Hotel, even if hotel space is not required by the registrant.

In order to provide for the widest possible distribution of the program, it will be included in a special section of October *Circulation*. Abstracts of many papers submitted for presentation at the Scientific Sessions will be printed in this section, which will then be reprinted for distribution in New Orleans.

APPLICATION DEADLINE FOR AHA FELLOWSHIPS IS SEPTEMBER 15

Applications for Association research investigatorships and fellowships for the fiscal year, July 1, 1956 through June 30, 1957, must be submitted by September 15. Applications for grants-in-aid covering the same period can be submitted through November 1, 1955.

Awards are made in the following categories:

Established Investigatorships: Awarded for periods of up to five years, subject to annual review, in amounts ranging from $6,000 to $9,000, to scientists of proven ability, who have developed in their research careers to the point where they are independent investigators.

Research Fellowships: Awarded to young men and women with doctoral degrees for periods of one to two years to enable them to train as investigators under experienced supervision. Stipends range from $3,500 to $5,600.

Grants-in-Aid: Made to experienced investigators to provide support for specific projects, in varying amounts up to $10,000.

The Association also maintains another and unique form of research support, the Career Investigatorship. This is awarded to a limited number of investigators of unusual capacity and accomplishment to assure them of financial support throughout their productive lives. Career investigators are selected from nominations made to the Research Committee, rather than by application.

Additional information and application blanks may be obtained from the Medical Director, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

LIFE INSURANCE FUND SETS RESEARCH AWARD DEADLINES

Announcement has been made by the Life Insurance Medical Research Fund of deadline dates for applying for fellowships and grants to take effect on July 1, 1956. The deadline for fellowship applications is October 15, 1955, and for grants, it is November 1, 1955.

Preference will be given to fellowship applicants working on cardiovascular function and disease or related fundamental problems. Minimum stipend for the post-doctoral fellowships will be $3,600 with allowances for dependents and necessary travel.

Grants will be made to institutions in aid of research on cardiovascular problems, including related physiological and biochemical projects. Full information and application forms may be obtained from the Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.

NEW EDITORS APPOINTED FOR 'MODERN CONCEPTS'

Three Portland, Ore., physicians will undertake editorial responsibility for *Modern Concepts of Cardiovascular Disease*, the Association's monthly bulletin for physicians, beginning on January 1, 1956.

Approval of the Association's Scientific Council has been given to the selection of Howard Lewis, M.D., as editor of the bulletin. His associates will be Herbert E. Griswold, Jr., M.D. and Franklin J. Underwood, M.D. They succeed Benedict Massell, M.D., Boston, the current editor, and Gordon S. Myers, M.D., also of Boston, who is the present associate editor.

BOOKLET DESCRIBES AHA SERVICES TO PROFESSION

"The American Heart Association Serves the Physician," a booklet listing and describing the professional services of the Association, is now available.

The booklet summarizes the research support program of the Association. It gives pertinent information on the availability of professional education aids prepared by the Association, in-

cluding films, audio-visual presentations, medical literature, heart models and charts. It also describes the periodical publications published by and for the Association.

Copies of "The American Heart Association Serves the Physician" may be obtained from your local Heart Association or from the AHA, 44 East 23 Street, New York 10, N. Y.

"CARDIAC CLINICS" OFFER HOME EDUCATIONAL OPPORTUNITIES

An audio-visual kit on the "Role of the P-A Film of the Chest in Cardiology" is now available from the Association. The kit is the first of the "Cardiac Clinics" series designed to enable physicians to continue their medical education at home, as well as for presentation in meetings and classes.

The first "Cardiac Clinic" was prepared by William R. Christensen, M.D., Professor of Radiology at the University of Utah College of Medicine. It consists of a medical discussion recorded on two 12-inch 33⅓ rpm long-playing records; a set of 39 slides correlated with the discussion; a script of the discussion; and a table-top viewer for the slides. The materials are contained in a rubber-lined carrying case. The only equipment needed by the physician is a 33⅓ rpm record player. Additional projection and amplification equipment is required to adapt the kit for group use.

The kit is available from the AHA and from a number of affiliated Heart Associations. Rental cost from the Association is $5.00 for three days plus railway express charges. Purchase price is $150. Two weeks should be allowed for delivery.

FIRST "CARDIO-VIEWS' 3-D KIT AVAILABLE

The first in the new Association series of three-dimensional visual kits, "Cardio-Views," is now available from the Association. The kit, entitled "Heart Models and Silhouettes," consists of 36 stereoscopic slides, descriptive stereo cards and a 3-D viewer. These slides present three views of each of 12 models of normal and abnormal hearts. Each slide also includes a cardiac silhouette representing a simulated x-ray picture, printed so that it projects above the 3-D viewer for easy comparison with the view on the slide.

The kit is suitable for use by practicing physicians, hospital staff, interns, residents and 3rd and 4th year medical students. The rental fee is $10. Kits can be obtained from the American Heart Association, 44 East 23 Street, New York 10.

VERMONT CARDIOVASCULAR SEMINARS SCHEDULED FOR SEPTEMBER 14–17

Two seminars, one on "Functional and Degenerative Heart Disease," and the other on "Electrocardiographic Diagnosis of Auricular and Ventricular Hypertrophy and Strain," will be conducted next month under the joint auspices of the Vermont Heart Association and the University of Vermont College of Medicine. Both seminars will be held in Burlington, Vt.

The heart disease seminar will be given by W. Raab, M.D., Professor of Experimental Medicine and Head of the Cardiovascular Research Unit at the University of Vermont College of Medicine. It will be held on Wednesday and Thursday, September 14 and 15.

The electrocardiographic diagnosis seminar will be led by Eugene Lepeschkin, M.D., Associate Professor of Experimental Medicine at the University of Vermont College of Medicine, on Friday and Saturday, September 16 and 17. Dr. Lepeschkin is an Established Investigator in the Association's research support program. Dr. E. Cabrera of the National Institute of Cardiology, Mexico City, will be a guest speaker.

Information on their respective seminars can be obtained from Drs. Raab and Lepeschkin at the University of Vermont College of Medicine, Burlington, Vt.

SCHEDULE ENZYMES SYMPOSIUM IN DETROIT NOVEMBER 1–3

An international symposium on the subject, "Enzymes: Units of Biological Structure and Function," will be held November 1–3 in Detroit under the auspices of the Henry Ford Hospital and the Edsel B. Ford Institute for Medical Research.

Among the subjects to be discussed in the symposium will be the origin of enzymes, the status of gene-enzyme relationship, the future of enzyme research, enzymes and cell structure, enzymatic basis of some physiologic functions, mechano-chemical coupling in muscle,

cellular energy sources and regulation of enzyme activity.

Participants will include Drs. Boris Ephrussi, Paris, France; Ernest F. Gale, Cambridge, England; Albert L. Lehninger, Baltimore; W. F. H. M. Mommaerts, Cleveland; Jacques Monod, Paris; Severo Ochoa, New York; Linus Pauling, Pasadena, Calif.; Thomas P. Singer, Detroit, and Albert Szent-Gyorgyi, Woods Hole, Mass.

For information, address inquiries to Dr. Clarence E. Rupe, Secretary, International Symposium on Enzymes, Henry Ford Hospital, Detroit 2, Michigan.

MEETINGS CALENDAR

Aug. 28–Sept. 2: Congress of Physical Medicine and Rehabilitation, Detroit. Francis Baker, 1 Tilton Ave., San Mateo, Calif.

Sept. 7–9: International Symposium on Arteriosclerosis, Minneapolis, jointly sponsored by University of Minnesota and Minnesota Heart Association. G. Ray Higgins, Executive Secretary, Minnesota Heart Association, 542 Endicott on Fourth, St. Paul 1, Minn.

Sept. 8–10: American Association of Obstetrics, Gynecology and Abdominal Surgery, Hot Springs, Va. F. R. Lock, Bowman Gray Medical School, Winston-Salem, N. C.

Sept. 12–14: Southwestern Surgical Congress, Kansas City. Dr. C. M. O'Leary, 207 Plaza Court Bldg., Oklahoma City.

Sept. 12–15: Congress of International College of Surgeons (U. S. and Canadian Sections), Philadelphia. Dr. Karl Meyer, 1516 Lake Shore Drive, Chicago 10.

Sept. 19–22: American Hospital Assoc., Atlantic City, N. J. Edwin L. Crosby, 18 E. Division St., Chicago 10.

Sept. 20–23: American Roentgen Ray Society, Chicago. Barton R. Young, Germantown Hospital, Philadelphia 44.

Oct. 10: College of American Pathologists, Chicago. Arthur H. Dearing, 203 N. Wabash Ave., Chicago.

Oct. 22–28: American Heart Association, 31st Annual Meeting and 28th Scientific Sessions, New Orleans. American Heart Association, 44 E. 23rd Street, New York 10.

Oct. 24–26: American College of Gastroenterology, Chicago. Joseph Shaiken, 33 W. 60th St., New York 23.

Oct. 27–29: American Association for Surgery of Trauma, Chicago. James K. Stack, 700 N. Michigan Blvd., Chicago 11.

Oct. 27–29: Gerontological Society, Baltimore. Nathan W. Shock, Baltimore City Hospitals, Baltimore, Md.

Oct. 29–Nov. 3: American Society of Anesthesiologists, Boston. J. E. Remlinger, Jr., 188 W. Randolph St., Chicago 1.

Oct. 31–Nov. 4: American College of Surgeons, Chicago. Michael L. Mason, 40 E. Erie St., Chicago 11.

Nov. 14–18: American Public Health Assoc., Kansas City, Mo. R. M. Atwater, 1790 Broadway, New York 19.

ABROAD

Aug. 14–20: Pan American Conference on Rheumatic Diseases, Rio de Janeiro and São Paulo, Brazil. Dr. Waldemar Bianchi, 126 Avenida Franklin D. Roosevelt, Rio de Janeiro.

Aug. 20–27: Australasian Medical Congress, Sydney, N.S.W., Australia. Federal Council of B.M.A. in Australia, 135 Macquaire Street, Sydney.

Aug. 21: World Federation for Mental Health, Istanbul, Turkey. Miss E. M. Thornton, World Federation for Mental Health, 19 Manchester Street, London W.1.

Sept. 1–4: International Medical Congress, Verona, Italy. Offices of the International Verona Fair, Piazza Bra., Verona, Italy.

Sept. 2–5: International Congress of Angiology and Histopathology, Fribourg, Switzerland. Dr. Gerson, 4 rue Pasquier, Paris 8.

Sept. 2–4: International Medical Congress, Evian, France. Dr. Laouênan, Directeur, Etablissement Thermal, Evian, France.

Sept. 5–10: World Congress of Anesthesiologists, Scheveningen, Netherlands. W. A. Fentener van Vlissingen, Noord-Houdringelaan, 24, Bilthoven, Netherlands.

Sept. 12–17: International Congress of Neuropathology, London. Dr. W. H. McMenemey, Department of Pathology, Maida Vale Hospital, London W. 9.

Sept. 20–24: International Congress of the European Society of Haemotology, Freiburg, Germany. Prof. Dr. Ludwig Heilmeyer, Hugstetter Strasse 55, Freiburg, Germany.

Sept. 20–26: Assembly of the World Medical Association, Vienna, Austria. Dr. Louis H. Bauer, 345 East 46 Street, N. Y. 17.

Oct. 13–15: Annual Meeting of Canadian Physiological Society, London, Ontario. Dr. J. M. R. Beveridge, Department of Biochemistry, Queen's University, Kingston, Ontario, Canada.

Oct. 28–29: International Congress of Bronchoesophagology, Buenos Aires. Dr. Juan Carlos Arauz, Cangallo 4015, Buenos Aires, Argentina.

Nov. 6–13: International Congress of Allergology, Rio de Janeiro. Dr. Bernard N. Halpern, 197 Blvd. St. Germain, Paris 7.

Nov. 7–12: International General Medical Congress, Rosario, Argentina. Dean Jose Imhoff, Santa Fé 3100, Rosario, Argentina.

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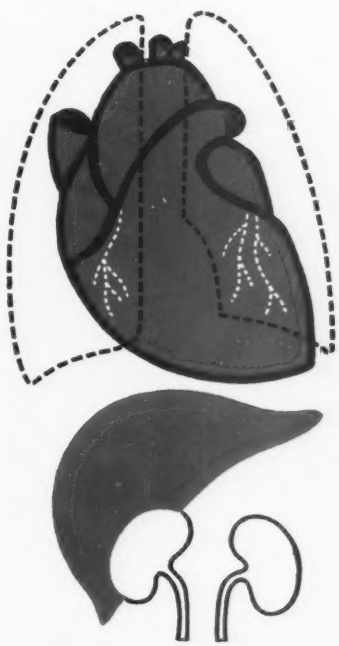

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